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Abstracts: ACC 24th Annual Scientific Session

Houston, Texas, February 10-13, 1975

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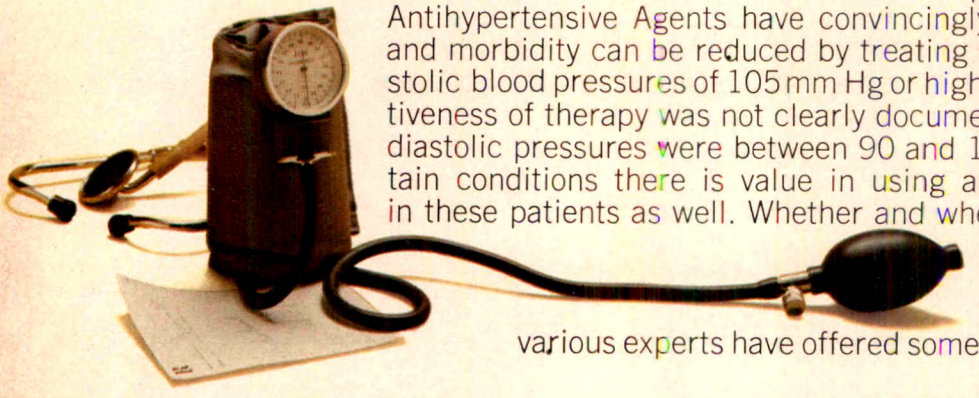
A YORKE MEDICAL JOURNAL

In the 90–104 mm Hg Diastolic Range—

When should medical management of hypertension include medication?



Data from the Veterans Administration Cooperative Study Group on Antihypertensive Agents have convincingly shown that mortality and morbidity can be reduced by treating patients with fixed diastolic blood pressures of 105 mm Hg or higher.[1] Although the effectiveness of therapy was not clearly documented in patients whose diastolic pressures were between 90 and 104 mm Hg, under certain conditions there is value in using antihypertensive agents in these patients as well. Whether and when to begin medication remains a matter of individual physician judgment. However, various experts have offered some useful guidelines.

Dr. Edward D. Freis, chairman of the VA Study Group, bases his decision on the following determining factors:[2]

Target Organ Damage

Such pathologic changes as retinopathy, left ventricular hypertrophy, and proteinuria are indications that hypertension is causing organic damage and should be treated immediately and aggressively.

Diabetes or Hypercholesterolemia

These diseases tremendously increase the risk of coronary disease, even in patients with modest blood pressure elevations.

Sex

Men have a higher risk than women of developing the complications of hypertension.

Race

Blacks tend to have earlier and more severe complications of hypertension than do whites.

Age

The younger the patient, the more hypertension will reduce his life expectancy.

Family History of Hypertension

If either parent had a major hypertensive complication, this adds significantly to the risk.

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg, JAMA *213*:1143, Aug 17, 1970.
2. Hypertension 1973: An expert draws the line on whom to treat, Patient Care *7*:63, April 15, 1973.
3. Kirkendall WM: What's with hypertension these days? Consultant *11*:13, Jan 1971.
4. Finnerty FA Jr: How to treat arterial hypertension, American Family Physician *7*:99, April 1973.

Kirkendall generally prefers to withhold medication when the sustained diastolic pressure is below 100 mm Hg unless "...a number of adverse factors exist, such as male sex, family history of vascular disease, youth, evidence of heart or kidney involvement."[3]

Finnerty finds it good practice to treat every patient whose diastolic pressure is persistently over 100 mm Hg. But he also says that "no definite statement can be made about the management of patients whose diastolic blood pressure averages between 90 and 100 mm Hg on repeated visits. If the patient is younger than 45 and there is a family history of hypertensive complications or the presence of end-organ damage (retina, heart, kidneys), treatment is probably indicated."[4]

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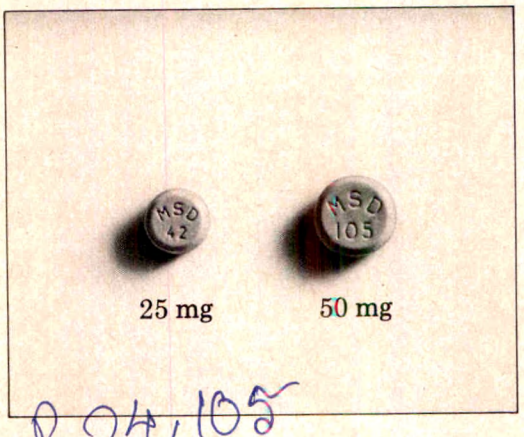

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia and cumulative effects may develop. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; the effect of discontinuance of therapy on serum calcium and phosphorus levels may be helpful in assessing the need for parathyroid surgery in such patients.

When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

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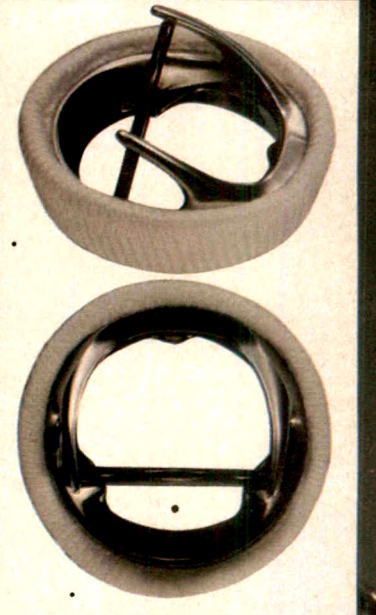

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3. Lillehei CW, et al: Heart Valve Replacement with the Lillehei-Kaster Pivoting Disc Prosthesis. Presented at the Southern African Cardiac Society 8th Biennial Cardiac Congress, 1972.
4. Lillehei CW, et al: A New Central Flow Pivoting Disc Aortic and Mitral Prosthesis: Initial Clinical Experience. Am J Cardiol 26:688, 1970.

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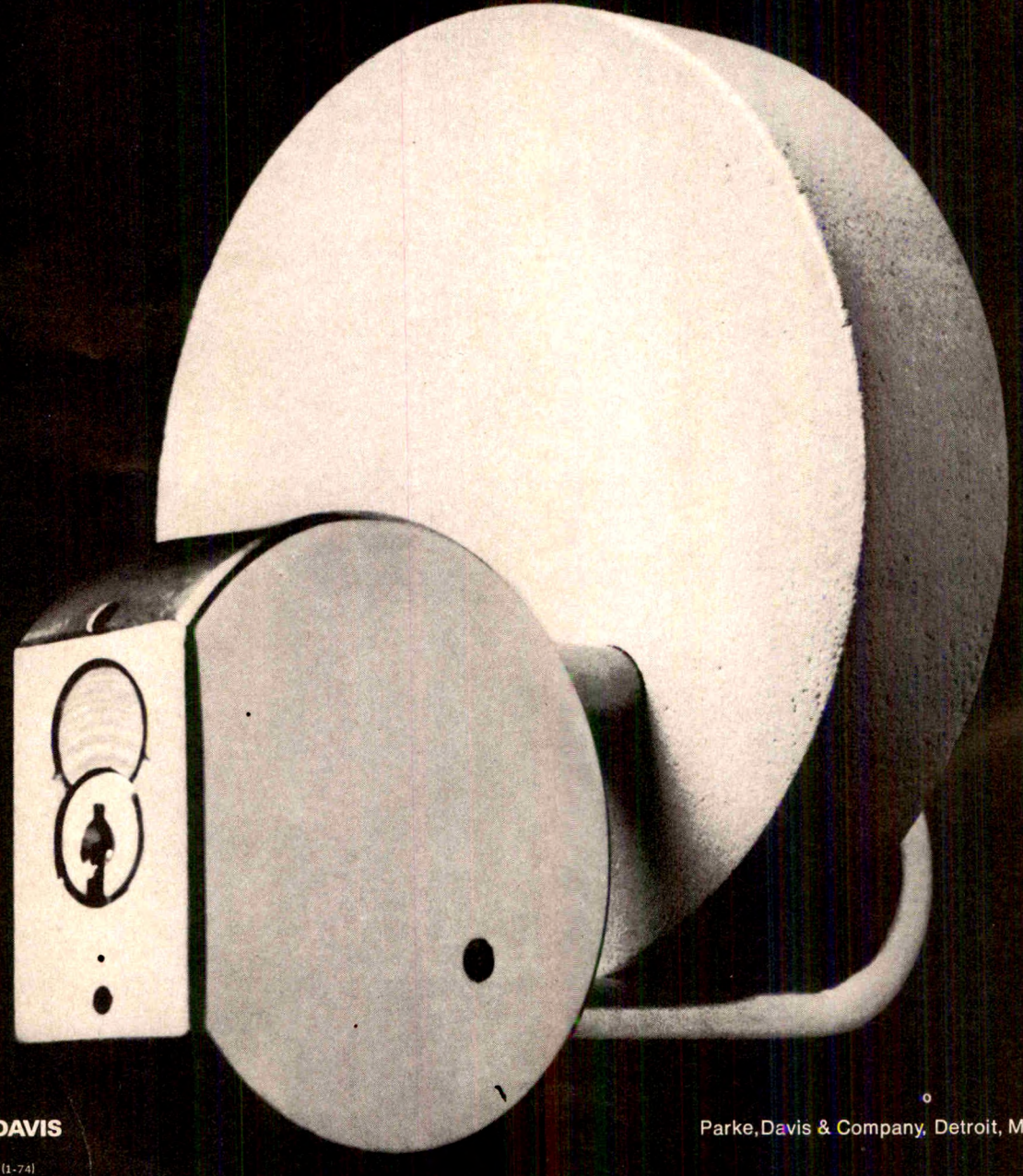

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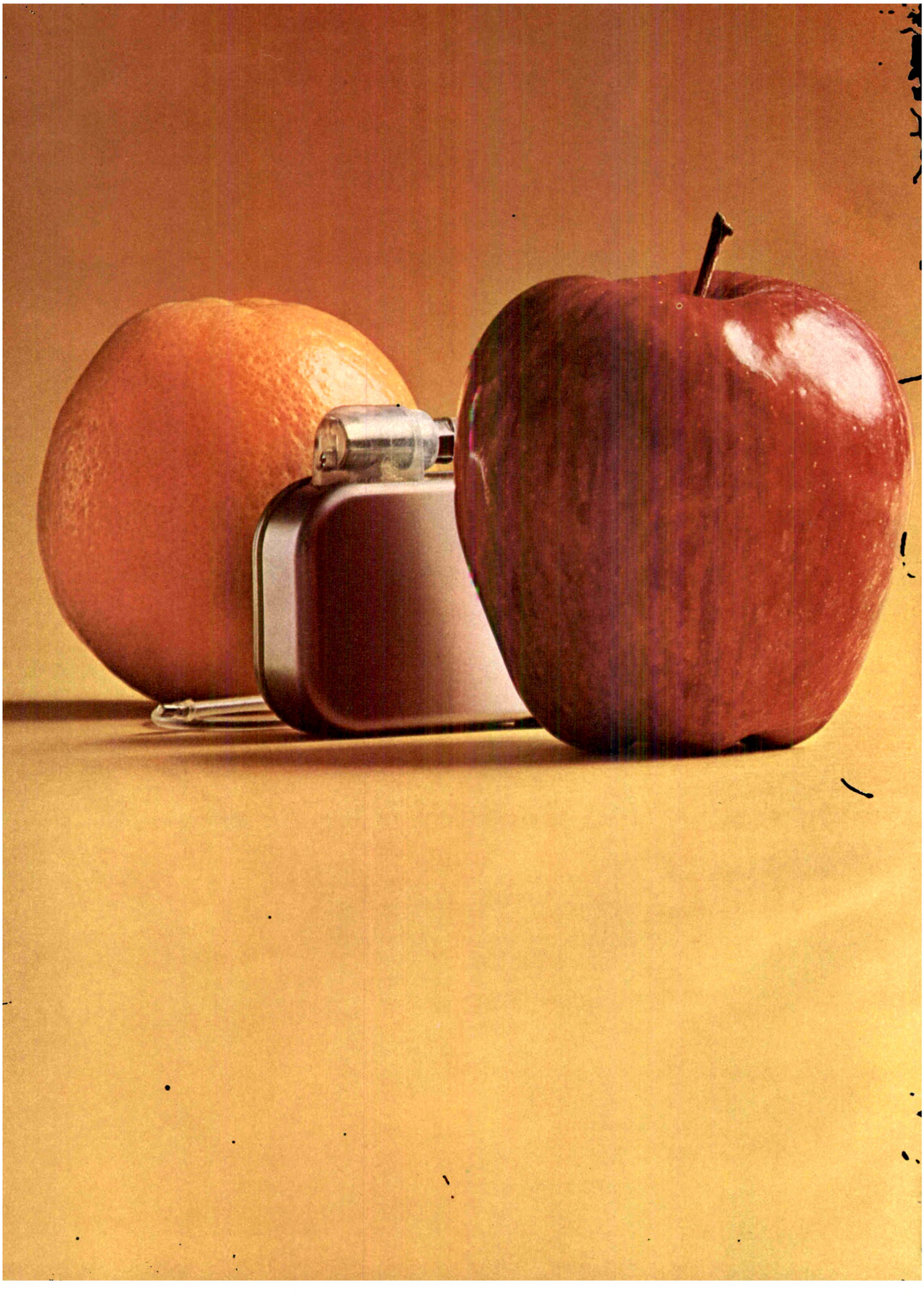

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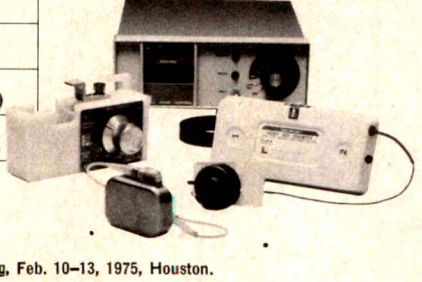

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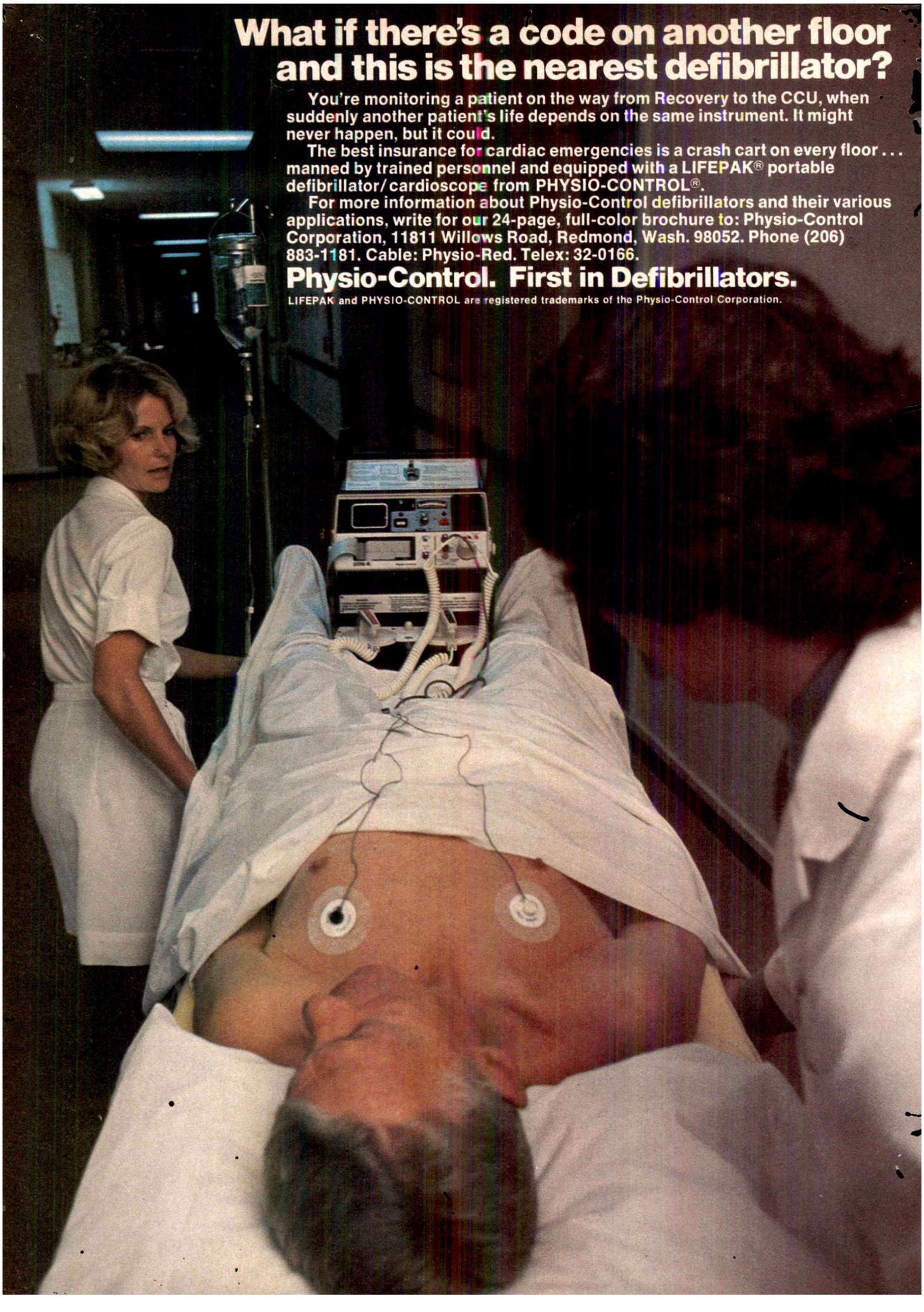
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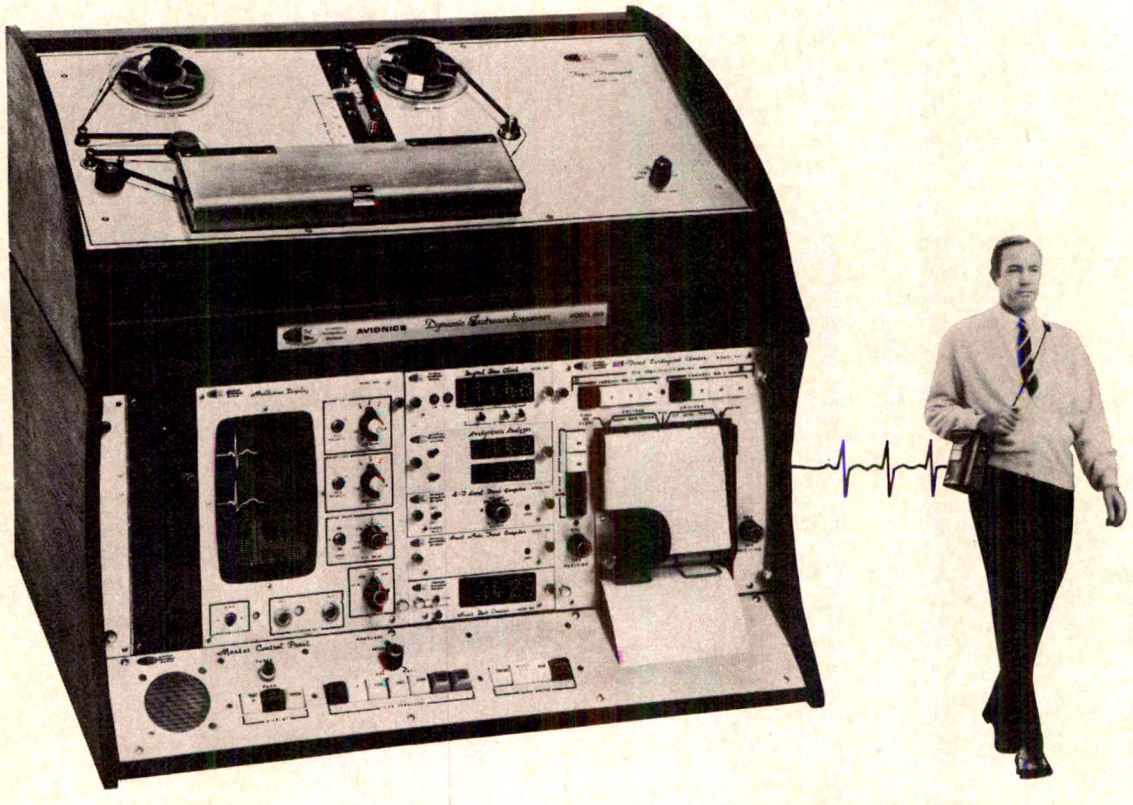

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JANUARY 1975

The American Journal of CARDIOLOGY®

VOLUME 35

NUMBER 1

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CLINICAL STUDIES

1 **Left Ventricular Function in Patients With and Without Myocardial Infarction and One, Two or Three Vessel Coronary Artery Disease**

ROGER E. MORASKI, RICHARD O. RUSSELL, Jr., McKAMY SMITH and CHARLES E. RACKLEY

Assessment of cardiac performance in patients with ischemic heart disease requires consideration of previous myocardial infarction and anatomic abnormalities of the coronary arteries. Data in 96 patients with ischemic heart disease show that in subjects with one, two or three vessel coronary artery disease a previous myocardial infarction significantly alters left ventricular performance and the ejection fraction is a more sensitive measurement of left ventricular function than left ventricular end-diastolic pressure or volume.

11 **Improvement of Reduced Left Ventricular Diastolic Compliance in Ischemic Heart Disease After Successful Coronary Artery Bypass Surgery**

RICHARD R. MILLER, ANTHONY N. DeMARIA, EZRA A. AMSTERDAM, MARY M. MAILANDER, ROBERT ZELIS, ARTHUR J. LURIE and DEAN T. MASON

By restoring coronary blood flow, successful coronary artery bypass surgery may increase ejection fraction and reverse depressed left ventricular diastolic compliance in certain patients with ischemic heart disease, particularly those without previous myocardial infarction. Increased ventricular stiffness is little affected by an open graft in patients with preoperative or intercurrent transmural infarction.

17 **Mechanism of the Bradycardia During Coronary Angiography**

RICHARD J. FRINK, BRUCE MERRICK and HAROLD M. LOWE

This study of 25 patients during coronary angiography demonstrates that angiographic dye decreases heart rate both by direct effect on pacemaker tissue and by reflex vagal suppression of the sinus pacemaker. Responses in type A patients, whose sinus and atrioventricular nodal arteries arose from the right coronary artery, differed from those in type B patients, in whom only the atrioventricular nodal artery arose from the right coronary artery.

23 **H-V Interval in Patients with Bifascicular Block (Right Bundle Branch Block and Left Anterior Hemiblock). Clinical, Electrocardiographic and Electrophysiologic Correlations**

PABLO DENES, RAMESH C. DHINGRA, DELON WU, RUBEN CHUQUIMIA, FERNANDO AMAT-Y-LEON, CHRISTOPHER WYNDHAM and KENNETH M. ROSEN

Electrophysiologic studies in 119 adults with chronic bifascicular block (right bundle branch block and left anterior hemiblock) revealed that a prolonged H-V interval was often associated with serious myocardial dysfunction and a high mortality rate. The risk of progression of conduction disease was slight with either a prolonged or a normal H-V interval within this relatively short follow-up period of 3 years.

Continued on page A13

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EXPERIMENTAL STUDIES

30 **Subendocardial Ischemia Provoked by Tachycardia in Conscious Dogs with Coronary Stenosis**

WILLIAM A. NEILL, JOHN OXENDINE, NANCY PHELPS and RICHARD P. ANDERSON

When reserve coronary vasodilatation has already been partially exploited in compensation for coronary stenosis, tachycardia induced in dogs with experimentally isolated stenosis of the left circumflex artery produces subendocardial ischemia and hypoxia as a result of increased extravascular coronary compression.

37 **Effects of Unipolar Cathodal and Bipolar Stimulation on Vulnerability of Ischemic Ventricles to Fibrillation**

WOLFGANG MERX, JAOK HAN and MYUNG S. YOON

The ventricular fibrillation threshold was significantly lower with both unipolar anodal and bipolar stimulation than with unipolar cathodal stimulation. Bipolar pacing is potentially more dangerous than unipolar cathodal pacing. The use of unipolar cathodal stimulation during acute myocardial infarction may reduce incidence of pacemaker-induced ventricular fibrillation.

PEDIATRIC CARDIOLOGY

42 **Double Outlet Right Ventricle {S,D,L} with Subaortic Ventricular Septal Defect and Pulmonary Stenosis. Report of Six Cases**

RICHARD VAN PRAAGH, CARLOS PÉREZ-TREVIÑO, JAMES L. REYNOLDS, C. A. F. MOES, JOHN D. KEITH, DOUGLAS L. ROY, CHRISTIAN BELCOURT, PAUL M. WEINBERG and LUCY F. PARISI

The data in these six cases of double outlet right ventricle characterized by situs solitus, ventricular *d*-loop and *l*-malposition of the great arteries, emphasizes the advisability of early surgical correction to minimize the progression of pulmonary infundibular stenosis and to avoid acquired atresia in these cases.

54 **Echocardiography in Atrioventricular Canal Defect. A Clinical Spectrum**

DANIEL R. PIERONI, EILEEN HOMCY and ROBERT M. FREEDOM

Echocardiographic data in 30 children with atrioventricular (A-V) canal defect demonstrate that this condition can be confidently diagnosed when all the following four types of A-V valve motion are observed: (1) anterior displacement of the typical M-shaped mitral valve motion, (2) traversing of the interventricular septum by the common anterior A-V leaflet, (3) abnormal tricuspid valve motion, and (4) double contour of the mitral leaflet during systole and marked duplication of the systolic image.

59 **Cor Triatriatum: Study of 20 Cases**

JOSÉ MARÍN-GARCÍA, RAJENDRA TANDON, RUSSELL V. LUCAS, Jr. and JESSE E. EDWARDS

Seven of these reported 20 cases of cor triatriatum (accessory chamber, common pulmonary vein, communication with the left atrium through one or more openings) were of the isolated type; 13 were associated with other cardiac anomalies. Pulmonary venous and arterial hypertension characterized the isolated type; various clinical findings and circulatory disturbances were noted in the patients with associated cardiac anomalies.

Continued on page A15

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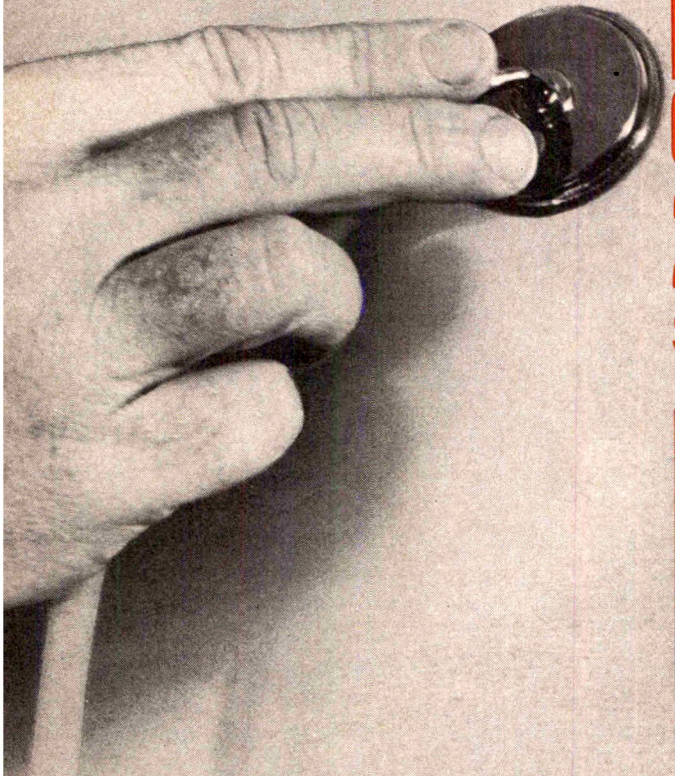

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REPORTS ON THERAPY

67 Clinical Implications of Warfarin Interactions with Five Sedatives

JOHN A. UDALL

These long-term self-controlled observations in human subjects indicate the inadvisability of administering barbiturates or glutethimide (Doriden) to patients receiving warfarin therapy since these agents accelerate coumarin metabolism and inhibit oral anticoagulant action. Chloral hydrate and methoqualone, on the other hand, do not clinically affect oral anticoagulant therapy and appear to be safe to use in such patients.

REVIEWS

72 Hemophilus Aphrophilus Endocarditis: Review of 23 Cases

SAMUEL K. ELSTER, LEONARD M. MATTES, BURT R. MEYERS and ROY A. JURADO

Although medical management alone may produce a salutary response in cases of bacterial endocarditis, surgical replacement of the aortic valve may be life-saving, as in this 40 year old man with Hemophilus endocarditis and congestive heart failure due to destruction of the aortic valve. This type of endocarditis with a high incidence of heart failure and systemic embolism has a high mortality rate despite the use of bactericidal drugs. Either complication may require early surgical intervention.

SPECIAL ARTICLE

80 Cardiovascular Investigations and Fuzzy Sets Theory

DANIEL KALMANSON and H. FRED STEGALL

"Fuzzy sets" are sets of elements or variables whose limits are ill-defined and imprecise. The concept of "fuzzy sets," as described, meets the needs of biological and clinical investigation for an alternative Heuristic decision-making path that permits the formulation of fuzzy concepts, fuzzy logic and even fuzzy algorithms which could be processed by fuzzy computers and lead to better understanding of complex biological phenomena. Examples are provided.

DIAGNOSTIC SHELF

85 Precordial Honk Due to Tricuspid Regurgitation

CHARLES B. UPSHAW, Jr.

Diagnostic maneuvers and cardiac catheterization clearly pinpoint tricuspid regurgitation as the origin of this wild goose honk in a 49 year old woman with cardiomyopathy and congestive heart failure. This case represents the third reported instance of systolic honk secondary to tricuspid regurgitation.

Continued on page A17

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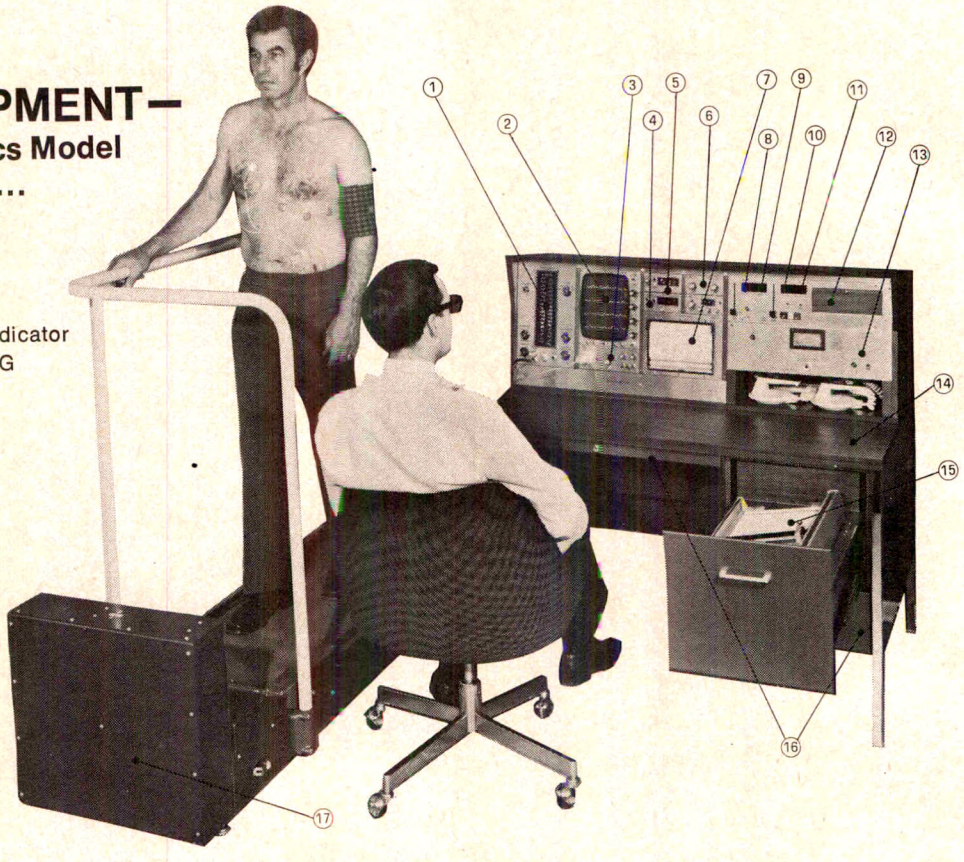

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MICHAEL R. SMITH, NEIL S. AGRUSS, NORMAN I. LEVENSON and ROBERT J. ADOLPH

This case report emphasizes the distinctive features of noninvasive techniques that distinguish asymmetric septal hypertrophy from apparent mitral stenosis and documents for the first time the presence and origin of an opening snap in intracardiac phonocardiograms in asymmetric septal hypertrophy.

CASE REPORTS

97 **Primary Cardiomyopathy in Identical Twins**

ALFONSO ANSELMI, JOSÉ ANGEL SUAREZ, GUILLERMO ANSELMI, FREDERICO MOLEIRO, CLAUDIA de SUAREZ and VICTOR RUESTA

Congenital primary cardiomyopathy, presumably arising from unknown teratogenic factors operative during early embryonic life, caused marked cardiomegaly, progressive heart failure and death within 5 months or less after onset of these symptoms in 17 year old identical twin brothers. Other members of the family were unaffected.

103 **Internal Mammary Arteriovenous Malformation with Communication to the Pulmonary Vessels**

EDWARD M. COHEN, DONALD E. LOEW and JOSEPH V. MESSER

As in the other five previously reported cases, hemodynamic alterations were minimal in this 25 year old asymptomatic heroin addict with a connection between a left internal mammary arteriovenous malformation and vessels in the left upper pulmonary lobe. This man declined surgical treatment.

107 **Progressive Pulmonary Vascular Disease After Surgical Correction (Mustard Procedure) of Transposition of Great Arteries with Intact Ventricular Septum**

RONALD ROSENGART, MICHAEL FISHBEIN and GEORGE C. EMMANOUILIDES

Despite an apparently successful Mustard intraatrial baffle operation, this 2 1/3 year old boy with transposition of the great arteries and intact ventricular septum died a year later from progressive pulmonary vascular disease. This late postoperative complication occurs more frequently than is generally recognized as a consequence of increased pulmonary perfusion pressure or blood flow and other factors.

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112 **Radionuclides and the Patient with Coronary Artery Disease**

BARRY L. ZARET and LAWRENCE S. COHEN

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116 **Letters to the Editor**

Surgical Correction of Double Outlet Right Ventricle—Kawashima and Doyle
Right Ventricular Infarction—Schwartz and Cohn

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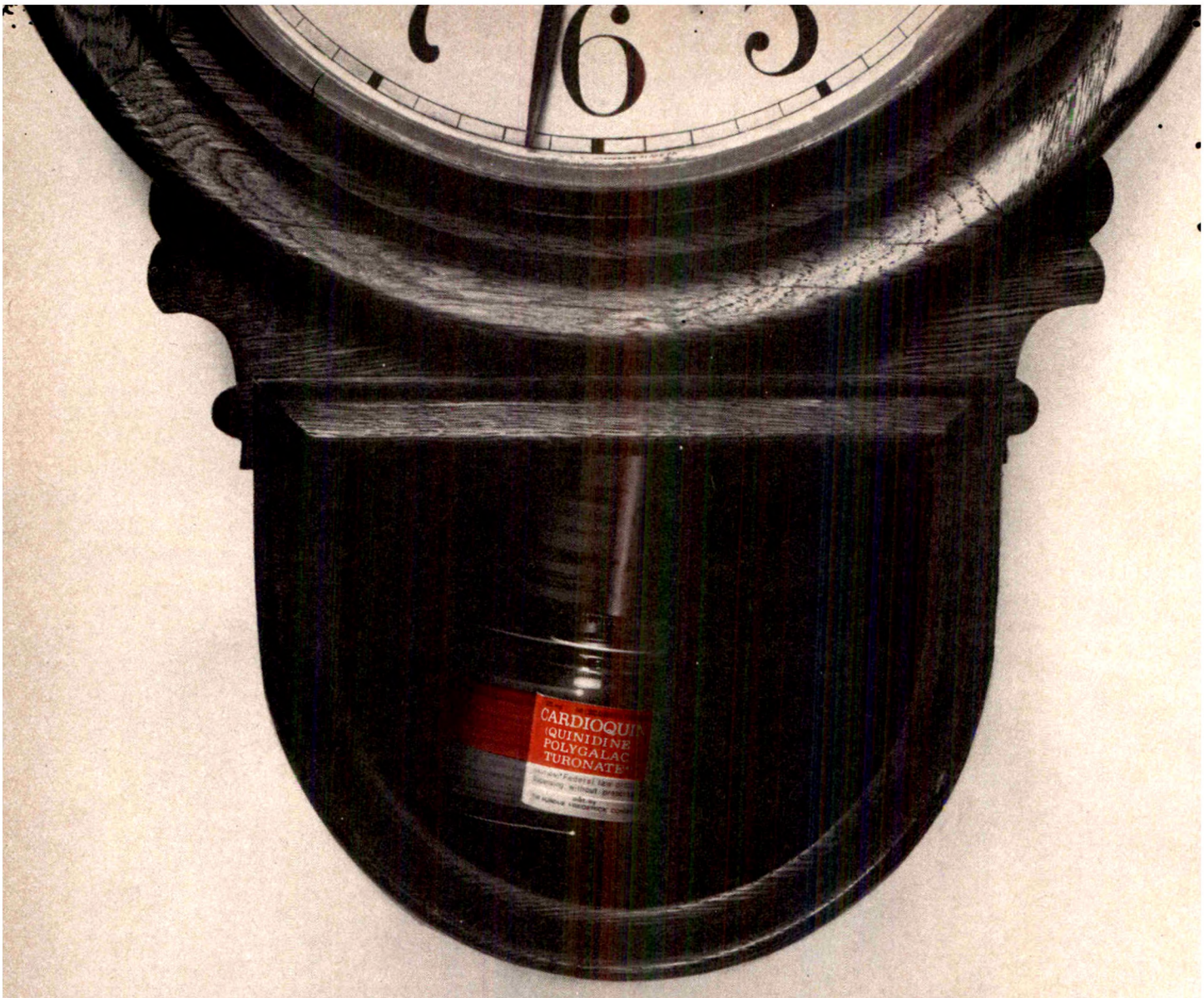

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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180 Author Index: Abstracts

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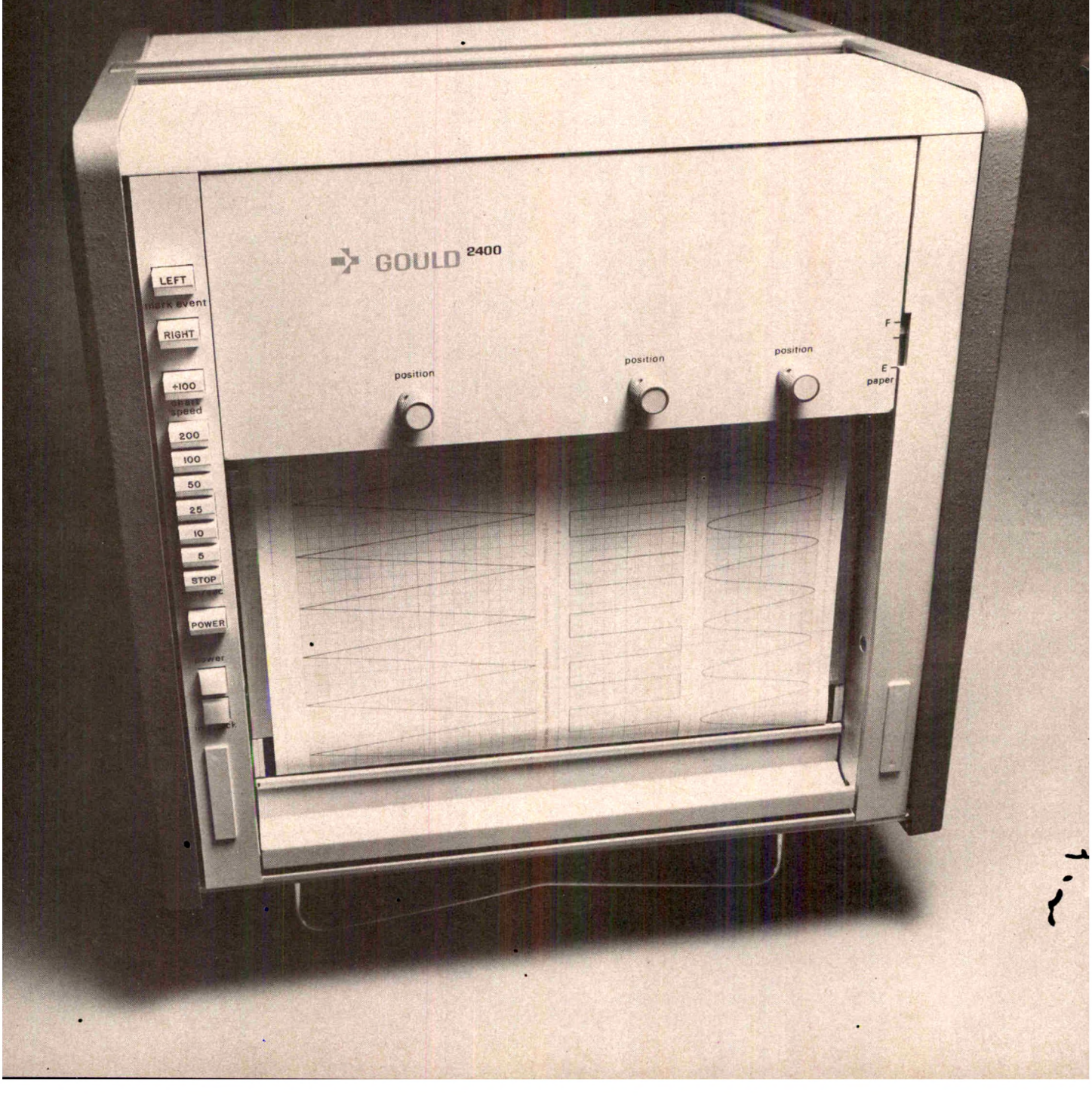

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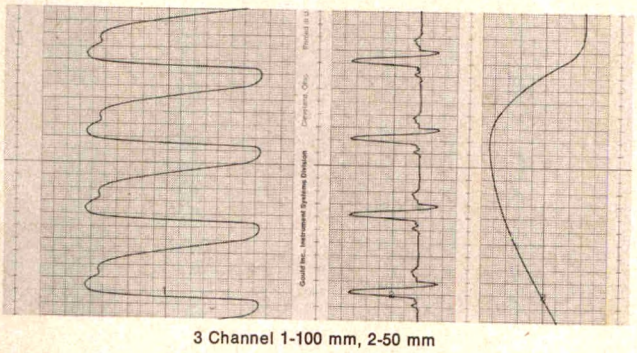

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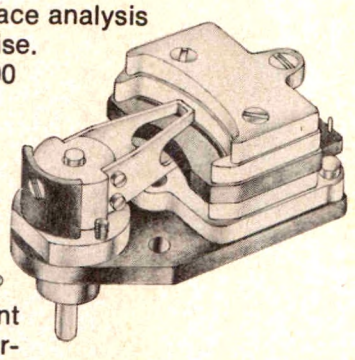

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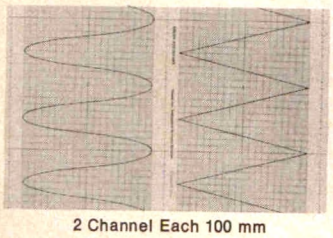

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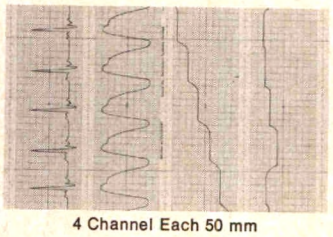

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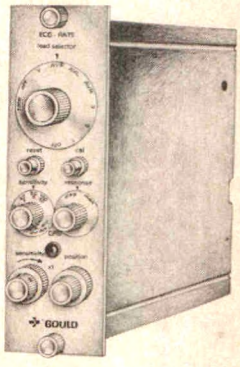

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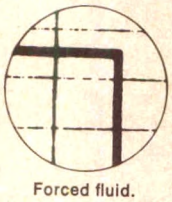

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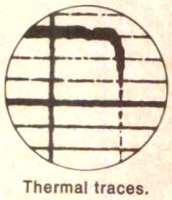

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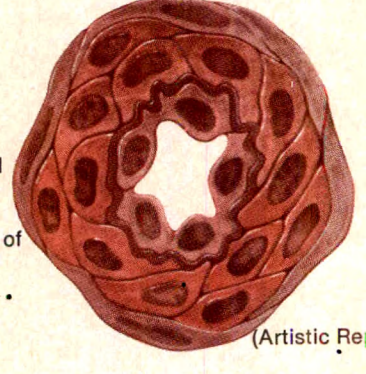

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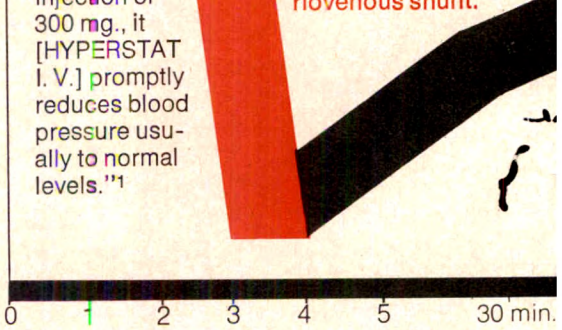

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Schering

Increases cardiac output—maintains coronary, cerebral blood flow—increased renal blood flow after initial decrease

HYPERSTAT I. V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system. However, as with any potent antihypertensive, it should be used with care in patients with impaired cerebral or cardiac circulation, in whom brief reductions in blood pressure might be detrimental.

Patients refractory to other antihypertensive agents usually remain responsive to HYPERSTAT I. V. Injection.

"The fall in arterial pressure with diazoxide is associated with an increase in cardiac output...a decrease in total peripheral resistance...and maintenance of cerebral blood flow..."[2]

Management of sodium and water retention, hypotension and hyperglycemia

Sodium and water retention, hypotension, or hyperglycemia may occur with HYPERSTAT I. V. Injection therapy.

Special attention is required for patients in whom retention of salt and water may present serious problems. In sodium retention, possible edema and congestive heart failure may be avoided with an appropriate diuretic, providing adequate renal function exists. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

Infrequent episodes of severe hypotension at recommended dosage or occasional undesirable hypotension from overdosage can usually be controlled with sympathomimetic drugs such as norepinephrine. Failure of blood pressure to rise in response to this agent suggests that the hypotension may be caused by

something other than HYPERSTAT I.V. Injection.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will usually respond to conventional management, including insulin.

References: 1. Gifford, R. W., Jr.: "Drugs For Arterial Hypertension" in Modell, W. (ed.): *Drugs of Choice 1972-1973*, St. Louis, The C. V. Mosby Company, 1972, p. 391. 2. Finnerty, F. A., Jr., *et al.*: Hypertensive Vascular Disease, The Long Term Effect of Rapid Repeated Reductions of Arterial Pressure with Diazoxide, *Am. J. Cardiol.*, *19*:377, 1967.

More than 1000 cases, over 12 years of clinical investigation in acute hypertensive situations support HYPERSTAT I.V. Injection usefulness in malignant hypertension

Twelve years of clinical experience with HYPERSTAT I. V. Injection confirmed its preclinical potential: to exert significant antihypertensive action through direct effect on peripheral arterioles which neither impairs cardiac output nor diminishes perfusion of kidneys.

In over 1000 cases, HYPERSTAT I. V. Injection proved useful for emergency reduction of blood pressure when prompt and urgent decrease of diastolic pressure was required.

Sustains relaxation of arteriolar muscle with no interference with compensatory autonomic mechanism.

(Artistic Representation)

hr. 4 hrs. 8 hrs. 12 hrs.

Injection activity up to 12 hours; individual response varies from patient to patient.

For emergency reduction of blood pressure in malignant hypertension

Direct-Action Hyperstat® I.V.

Brand of DIAZOXIDE

INJECTION
20 ml ampule
contains 300 mg.

In hospitalized patients when there's pressure for immediate control

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

DESCRIPTION HYPERSTAT I.V. Injection is a rapidly acting antihypertensive agent. Each ampule (20 ml.) contains 300 mg. diazoxide, a nondiuretic benzothiadiazine derivative, in a clear, colorless, aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide. Diazoxide is 7-chloro-3-methyl-2H 1, 2, 4-benzothiadiazine 1, 1-dioxide.

ACTIONS HYPERSTAT I.V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system.

Patients refractory to other antihypertensive agents usually remain responsive to diazoxide.

Diazoxide is extensively bound to serum protein (>90%). The plasma half-life is 28 ± 8.3 hours; however, the duration of its antihypertensive effect is variable, generally lasting less than 12 hours. Although an antihypertensive response has been obtained with slow intravenous injection, in general, a greater antihypertensive effect is obtained with rapid intravenous administration.

INDICATIONS HYPERSTAT I.V. Injection is indicated for the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled.

HYPERSTAT I.V. Injection is ineffective against hypertension due to pheochromocytoma.

CONTRAINDICATIONS HYPERSTAT I.V. Injection should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt.

The drug should not be used in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

WARNINGS **Usage in Pregnancy:** The safety of HYPERSTAT I.V. Injection in pregnancy has not yet been established.

Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults.

Usage in Children: The safety of HYPERSTAT I.V. Injection in children has not yet been established.

Hypotension may occasionally result from the administration of HYPERSTAT I.V. If hypotension severe enough to require therapy occurs, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide.

Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. It should be noted that concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions).

Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent.

Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

PRECAUTIONS HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available when HYPERSTAT I.V. Injection is used.

HYPERSTAT I.V. Injection should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively.

Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response.

As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental.

Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection.

Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

ADVERSE REACTIONS

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial and/or cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; unconsciousness, convulsions, paralysis, or confusion; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported.

Other adverse reactions: Nausea, vomiting, and/or abdominal discomfort; vasodilative phenomena, such as flushing, generalized or localized sensations of warmth, headache (sometimes throbbing), and sweating; orthostatic hypotension, lightheadedness and weakness of short duration; supraventricular tachycardia and palpitation; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; nonanginal "tightness in the chest"; warmth or pain along the injected vein; cellulitis without sloughing and/or phlebitis at the site of extravasation; anorexia and alteration of taste; ileus; bradycardia; back pain; chest discomfort; dyspnea, choking sensation; apprehension or anxiety, malaise, and blurred vision occurred on single occasions; paro swelling, salivation, lacrimation; ringing in the ears; diarrhea and constipation; increas nocturia; euphoria.

DRUG INTERACTIONS Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

OVERDOSAGE Overdosage of HYPERSTAT (diazoxide) I.V. Injection may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agen suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy hyperglycemia.

Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In studies involving a number of species, including the rat, cat, dog, and monkey, diazoxide has been shown to exert significant antihypertensive actions through its direct effect on peripheral arterioles, which neither impairs cardiac function nor seriously diminishes perfusion of kidneys. In addition, in each species tested, including the rat, dog, and monkey, diazoxide elicits hyperglycemia, increased serum-free fatty acids and decreased plasma insulin levels by a mechanism thought to involve both suppression of insulin release and enhanced catecholamine actio

Although the data are not conclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term.

DOSAGE AND ADMINISTRATION HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injection. It should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

The response to HYPERSTAT I.V. Injection varies from patient to patient. Generally, bloo pressure decreases within five minutes, often within one to two minutes, to the lowest lev achieved. The blood pressure increases relatively rapidly in the next ten to 30 minutes, an then more slowly over the following two to 12 hours, nearly reaching but rarely exceeding the pretreatment level. The response to successive injections is frequently better than tha to the initial injection.

Treatment of hypertensive emergencies with HYPERSTAT I.V. Injection should be limited to a few days and a regimen of oral antihypertensive medications should be instituted a soon as possible.

With the patient recumbent, the contents of one 20 ml. ampule containing 300 mg. of HYPERSTAT I.V. Injection are administered intravenously in 30 seconds or less. Slow intravenous injection may fail to reduce the blood pressure or may produce an exceedingly short response.

Specific dosage is required in children or in unusually large or small patients. This dosage may be calculated on the basis of 5 mg./kg. body weight (0.3 ml./kg.) (See Warnings).

A second administration of HYPERSTAT I.V. Injection may be required for a satisfactory reduction in blood pressure, if the first injection fails to give an adequate response within 30 minutes.

Repeated administration of HYPERSTAT I.V. Injection at intervals of four to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication becomes effective. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect will indicate any unusual response. A further decrease in blood pressure at 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain recumbent for half an hour after injection. In ambulatory patients, the blood pressure should be measured with the patient standing before surveillance is ended.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive failure.

HOW SUPPLIED HYPERSTAT I.V. Injection is supplied in a 20 ml. ampule containing diazoxide 300 mg. in a clear, colorless aqueous solution; box of one ampule.

Protect from light and freezing.

Store away from heat.

AUGUST 1973

20 ml.
in 30 seconds
for direct action

Schering

Schering Corporation
Kenilworth, N. J. 07033

SWW-383

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For a full color brochure on this comprehensive new system, write: Marquette Electronics, Inc., Suite 121, P.O. Box 8039, 8200 West Tower Avenue, Milwaukee, Wisconsin 53223.

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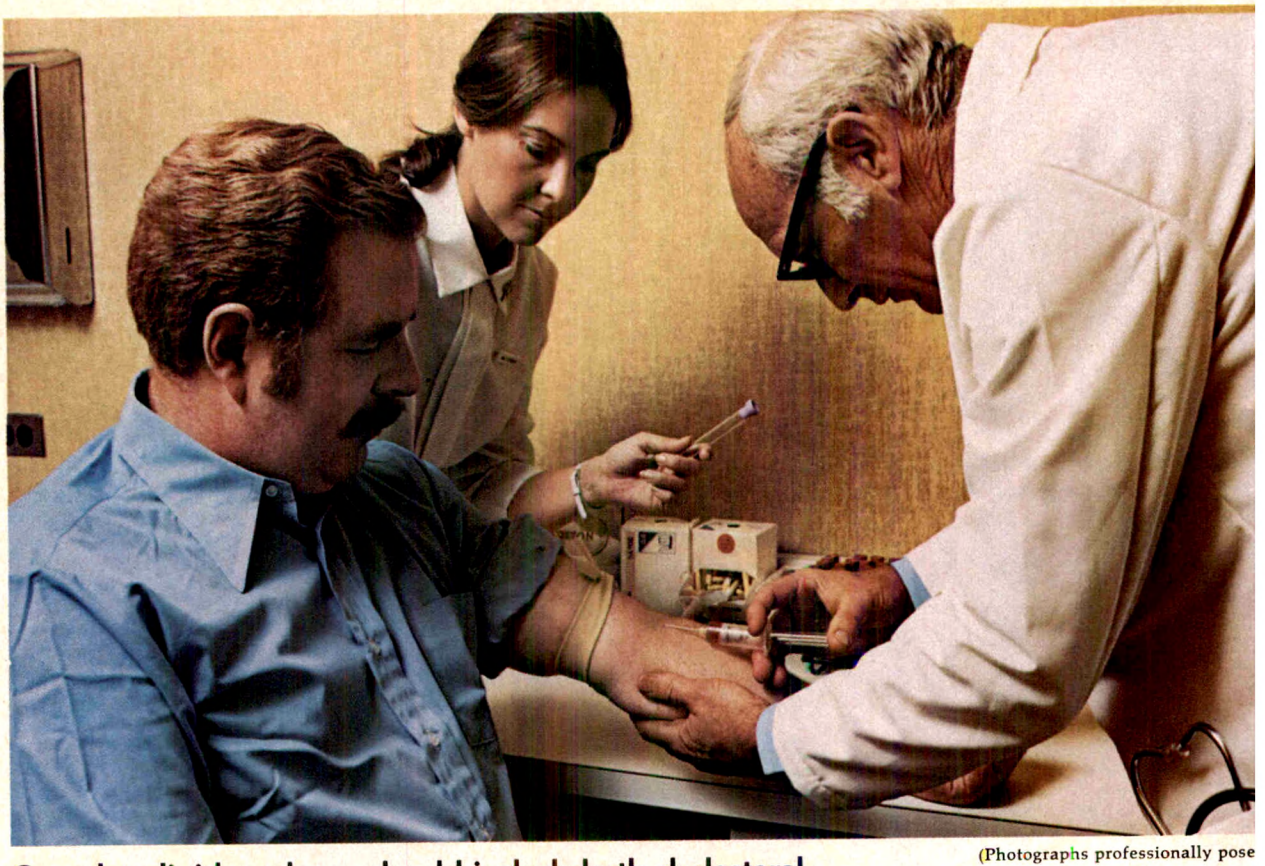
"Hyperlipidemia is one of several factors I search



(Photographs professionally pose

Complete lipid work-up should include both cholesterol and triglyceride determinations

Testing for both lipids—rather than just for cholesterol alone—increases the chances of detecting hyperlipidemia from 60% to over 95%.[2]

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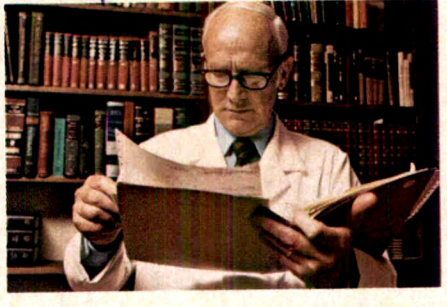
Lab results indicate pattern of lipid abnormality

When initial determinations of fasting serum cholesterol and triglyceride levels indicate the presence of hyperlipidemia, the pattern of the lipid abnormality should also be determined.[3]

When lipid elevations are confirmed, underlying disease states that may alter lipid metabolism should be ruled out through history, physical examination, and appropriate laboratory tests. Effective treatment of these pathologic conditions, if they exist, will often return the elevated lipids to a normal range. In the absence of an underlying cause, elevated lipid levels indicate a primary hyperlipidemia.



Therapy begins–but does not necessarily end–with specific dietary recommendations

Diet (specific for the lipid abnormality) is the starting point in the management of primary hyperlipidemia, and in the relatively rare Type I hyperlipoproteinemia it is the *only* therapy since currentl available drugs are ineffective. But in the drug-responsive types (Types IIa, IIb, III, IV and V) diet alone may fail to lower lipids adequately.

Drug therapy is often necessary as an adjunct to di

Convincing the asymptomatic hyperlipidemic patient to give up his favorite foods for benefits he may not feel is, at best, a difficult task. Even under carefully monitored dietary regimens, lipid reductions may be inadequate.[4] For the reasons it is often necessary to add an antilipemic agent to the dietary regime to produce a significant reduction in serum lipids.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

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or and vigorously treat."[1]

Along with early hypertension, excessive igarette smoking and dietary indiscre-ions, it is one of the few manifestations f modern society that an individual hysician can attempt to control."[1]

This is how one clinician views hyper-ipidemia—a condition widespread in merica today. The treatment he speaks f often calls for a dietary regimen spe-ific for the lipid abnormality *plus* an ntilipemic agent. And since many hy-erlipidemic patients exhibit elevations f *both* cholesterol and triglycerides, hey need a drug such as ATROMID-S clofibrate), which has the ability to ower *both* lipids.

tromid-S significantly reduces choles-erol and triglycerides—even in diet-esistant patients

ATROMID-S as an adjunct to diet has proven record of effectiveness in lower-ng serum elevations of both cholesterol nd triglycerides.

Cholesterol levels above 250 mg.% ave decreased as much as 35%, nd reductions up to 50% have been eported.[5-8] Triglyceride levels above 50 mg.% have decreased as much as 1%, and reductions up to 90% have een reported.[5,8] Patients resistant to iet alone have also experienced signifi-nt lipid lowering on ATROMID-S.

Although most hyperlipidemic pa-ents are asymptomatic, a small number ay exhibit skin lesions or xanthomas. egression of xanthomatous lesions with TROMID-S visually demonstrates the efficacy of this lipid-lowering agent. In some patients xanthomas disappear completely. In others the size and number of lesions are reduced.

Continuous treatment, maintenance of daily dosage vital to long-term control

Reliable cholesterol- and triglyceride-lowering effect is usually sustained as long as ATROMID-S treatment is uninterrupted. This ability to maintain control of serum lipids for extended periods is of primary importance in treating a disorder as persistent as hyperlipidemia.

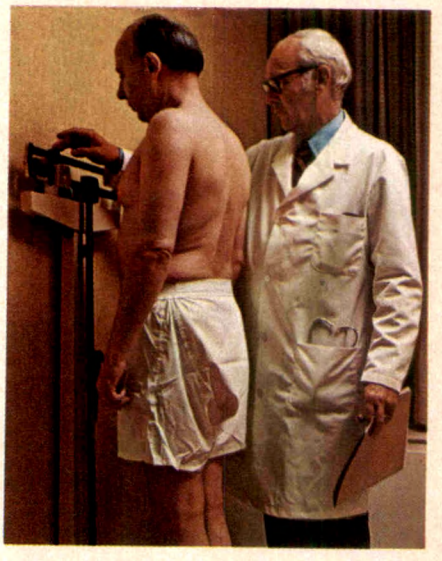
ATROMID-S is effective in a simple, well-accepted regimen that patients can stay with. Initial *and* maintenance dosage is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. To maintain continuous control of lipid levels, therapy should be uninterrupted.

The lipid-lowering effect of ATROMID-S is usually noted during the first month of therapy. The higher the initial level, the greater the lipid reduction likely to occur.

If response is inadequate after three months of therapy, the drug should be discontinued. However, if xanthoma tuberosum is present, treatment should continue for longer periods (even up to one year) provided there is a reduction in the size and/or number of the xanthomas.

10 years of successful overall clinical experience with Atromid-S

Throughout more than ten years of widespread use, ATROMID-S has proven to be an effective and very well-tolerated drug. However, before prescribing, you should be thoroughly familiar with the possible adverse reactions as well as with the precautions and warnings described on the last page of this advertisement.



Periodic follow-up important

Once blood lipids have been stabilized at normal levels on a regimen of diet and ATROMID-S, the patient should be examined and his blood lipids tested every two to three months during the first year or so. If stabilization at such lower levels is maintained over this period, the intervals between measurements can be lengthened.

Atromid-S®

Brand of clofibrate

helps control the lipid factor in your patient's profile

Ayerst®

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

See last page of advertisement for prescribing information.

Atromid-S® (clofibrate)
helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone

Initial and maintenance dosage: 2 Gm. daily (four capsules), in divided doses. Some patients may respond to a lower dosage.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
ATROMID-S® (clofibrate)
Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (Sf 20-400) rich in triglycerides than the low density lipoproteins (Sf 0-20) rich in cholesterol.
ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.
It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.
It is contraindicated in patients with clinically significant hepatic or renal dysfunction.
It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.
Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.
Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.
Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.
During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. Hepatic biopsies are usually within normal limits. These effects are usually reversible when the drug is discontinued. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.
Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.
Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.
Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.
Various cardiac arrhythmias have been reported with the use of clofibrate.
Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.
The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. *Maintenance:* Same as for initial dosage. **Note:** In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. La Bree, J., M.D. (Director of Medical Education, St. Mary's Hosp., Minneapolis, Minn.): Unraveling the Metabolic Mysteries Affecting Diagnosis and Therapy, Ayerst Laboratories, 1972, p. 13. **2.** Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, New York, Plenum Press, 1969, vol. 4, p. 314. **3.** Levy, R. I., in Conn, H. F.: Current Therapy 1973, Philadelphia, Saunders, 1973, p. 267. **4.** Parsons, W. B., Jr.: Clin. Med. *78*:15 (Nov.) 1971. **5.** Gelfand, M. L., and Garber, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. **6.** Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. **7.** Zelis, R., *et al.*: J. Clin. Invest. 49:1007 (May) 1970. **8.** Levy, R. I., and Fredrickson, D. S.: Am. J. Cardiol. 22:576 (Oct.) 1968.

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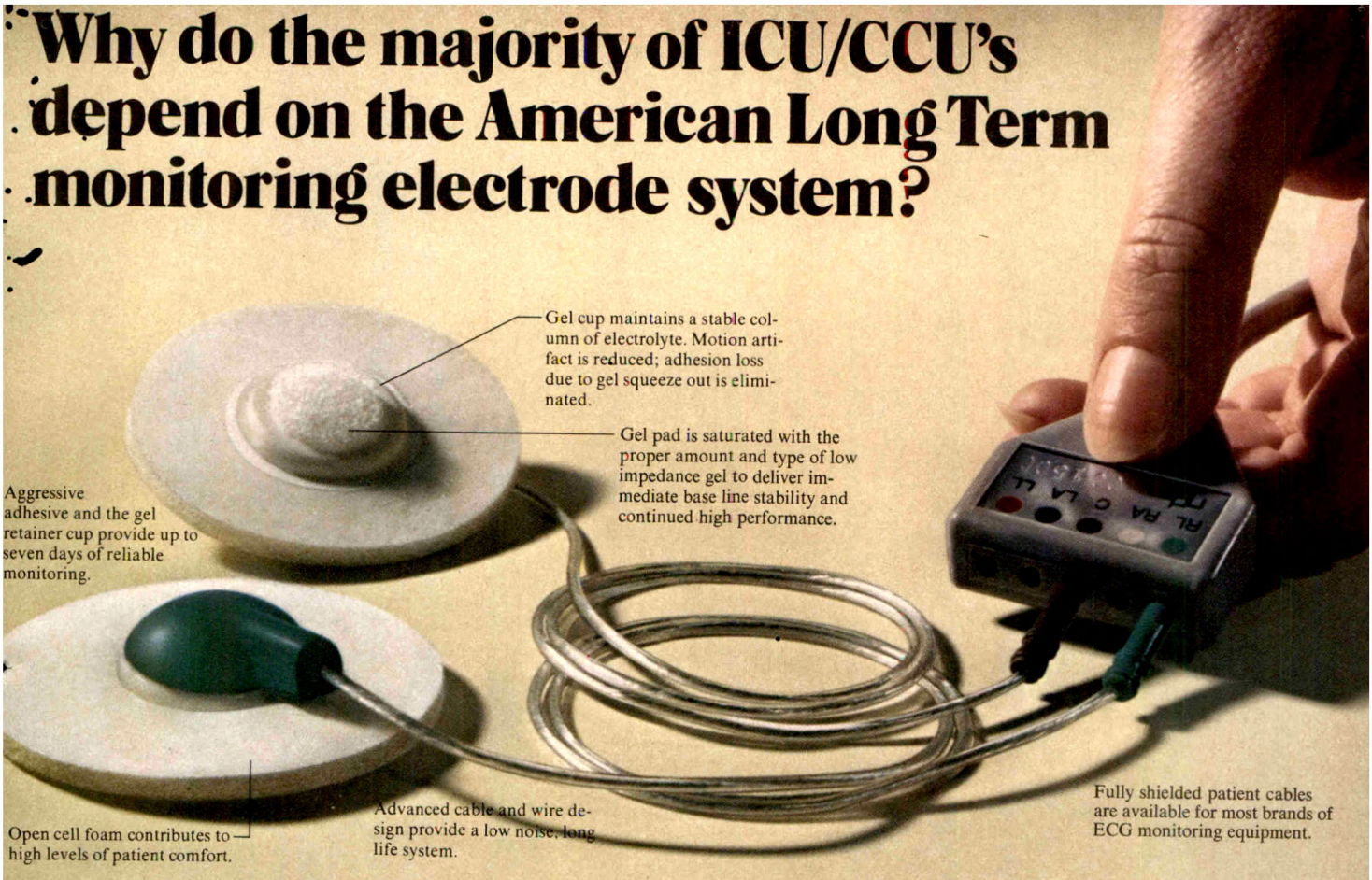
7458

Why do the majority of ICU/CCU's depend on the American Long Term monitoring electrode system?



This is the system that has established new standards for high performance in long term ECG monitoring.

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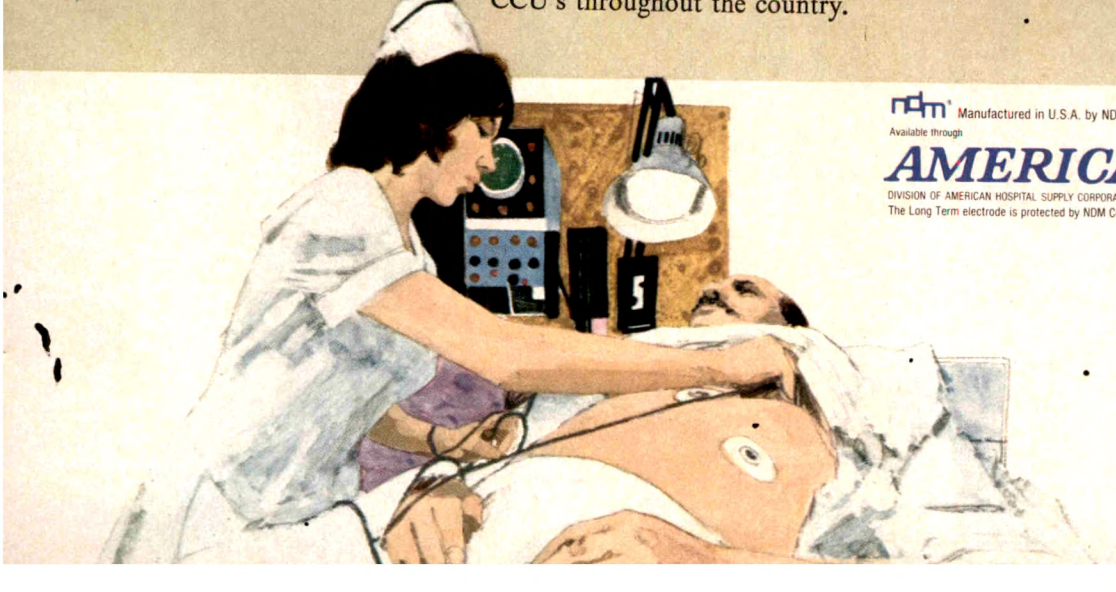
Open cell foam complements the electrode's mild gel formulation and low profile to enhance patient comfort. When used as directed, American's Long Term Electrode provides from five to seven days of continuous, accurate monitoring . . . with no discomfort to the patient.

This advanced electrode, used with the appropriate American leadwire and cable, is fully compatible with your present ECG equipment.

A clinical trial will show you why the American Long Term Electrode system is the overwhelming choice of ICU/CCU's throughout the country.

Please contact your American Hospital Supply or NDM representative and ask for:

- A demonstration of the system's benefits.
- A no obligation clinical trial. American will supply electrodes, leadwires and cables to adapt to your present monitoring equipment during the trial period.
- A total inservice for your staff.
- Information about our nationwide technical support program.



ndm Manufactured in U.S.A. by NDM Corporation, Dayton, Ohio 45439

Available through

AMERICAN HOSPITAL SUPPLY

DIVISION OF AMERICAN HOSPITAL SUPPLY CORPORATION • General Offices: 1450 Waukegan Road, McGaw Park, Illinois 60085

The Long Term electrode is protected by NDM Corp. by the following U.S. Patents: 3,696,807; 3,701,346; 3,713,435.

AMERICAN HOSPITAL SUPPLY

Introducing EX BIER® new from Switzerland

Alcohol is removed after it's been brewed and aged.

Looks and tastes just like great imported beer but has 60% less calories.*

*59 calories per 11½ ounces.

For more information visit booth 716

or write: Package Distributors of America, Inc.
1345 Avenue of the Americas
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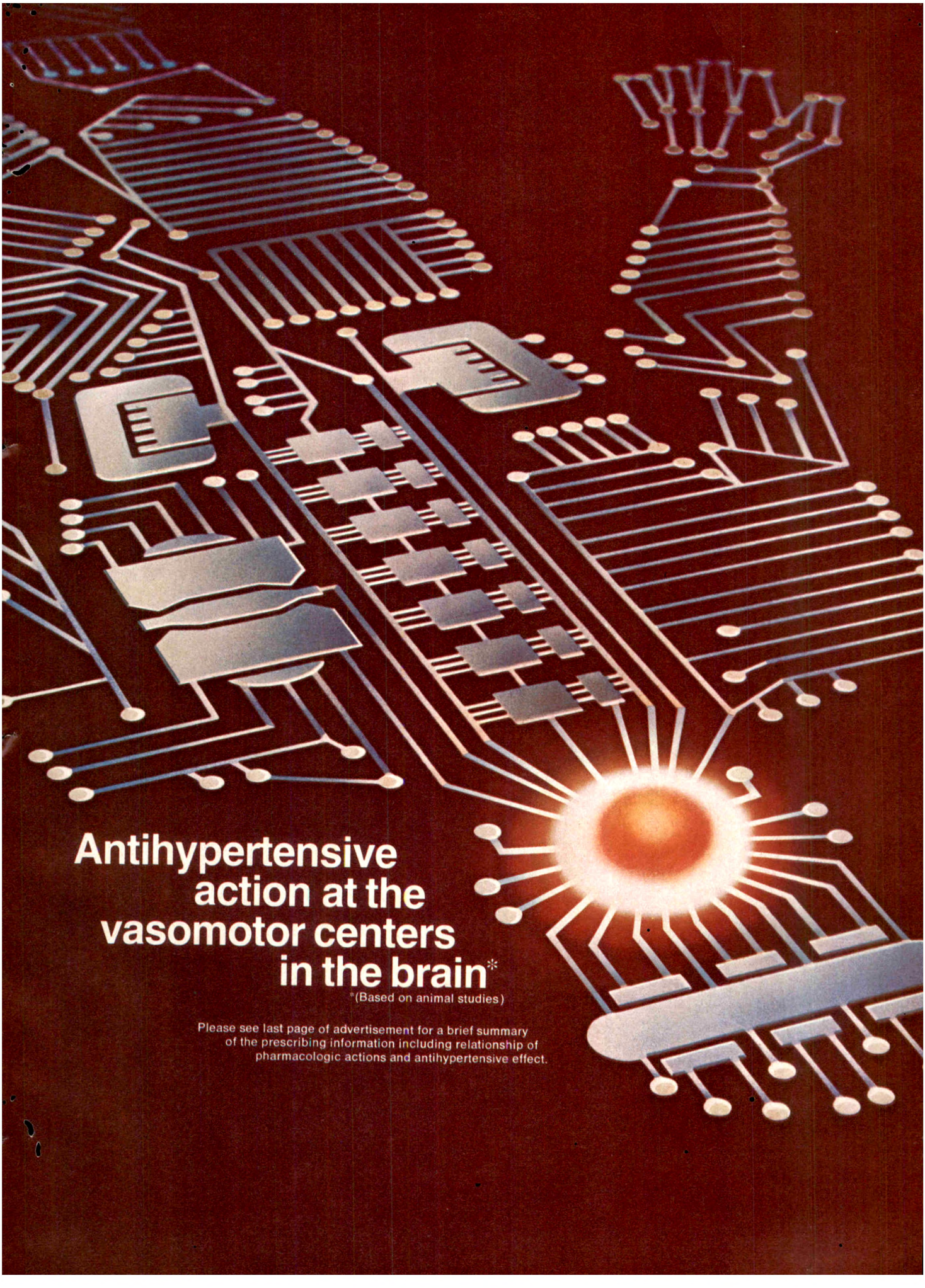

Antihypertensive
action at the
vasomotor centers
in the brain*
*(Based on animal studies)
Please see last page of advertisement for a brief summary
of the prescribing information including relationship of
pharmacologic actions and antihypertensive effect.

Now... antihypertensive action at the vasomotor centers in the brain

new Catapres®

Tablets of 0.1 and 0.2 mg

(clonidine hydrochloride)

Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

Central action:

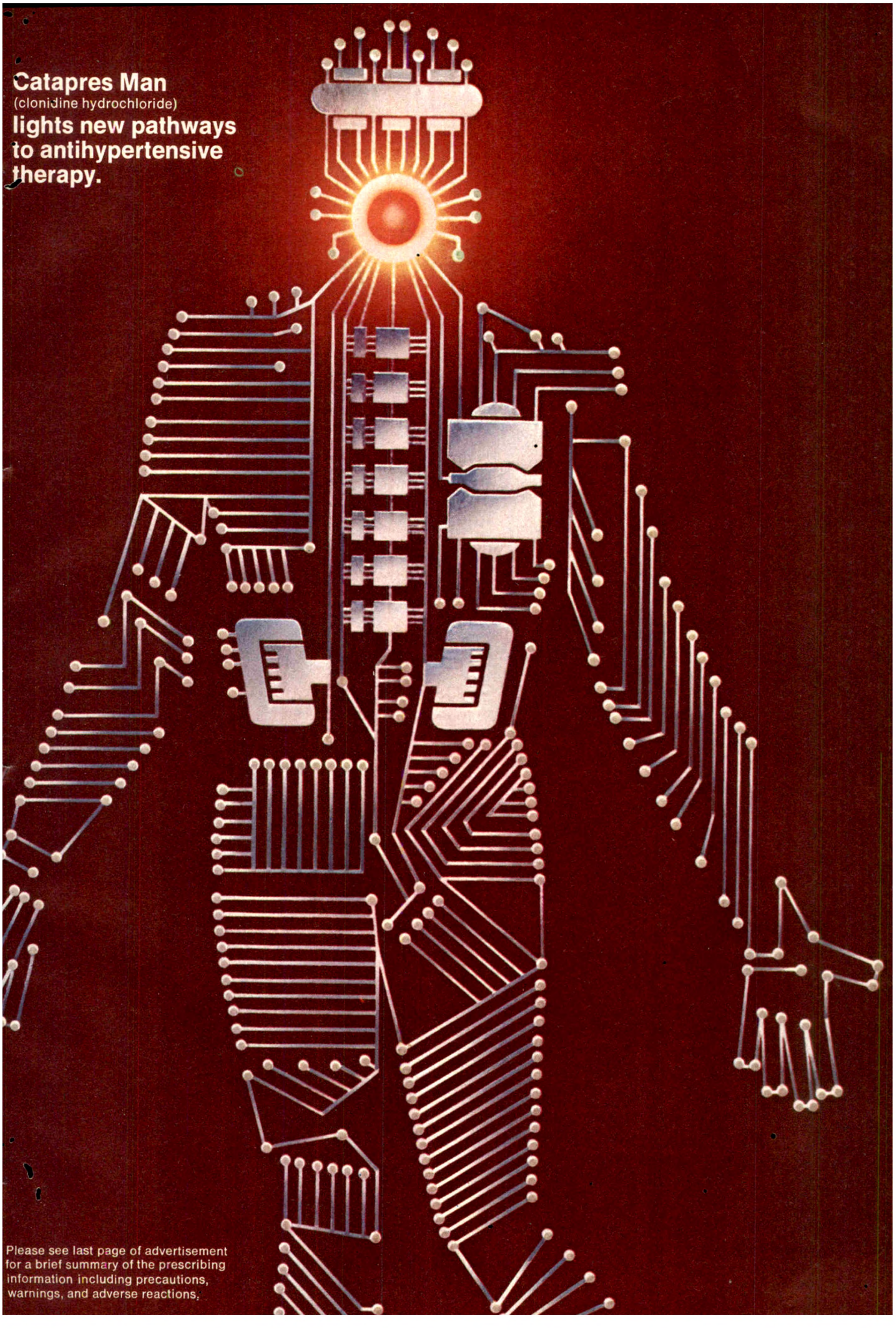
Catapres appears to lower blo pressure through central alpha adrenergic stimulation, as sho in animal studies. This results diminution—but not blocking— sympathetic outflow from card accelerator and vasoconstricto centers in the medulla.

Not a "depleter"

Not a "blocker"

Not an "inhibitor"

Not a "false transmitter"


Catapres Man
(clonidine hydrochloride)
lights new pathways
to antihypertensive
therapy.
Please see last page of advertisement
for a brief summary of the prescribing
information including precautions,
warnings, and adverse reactions.

new Catapres®
(clonidine hydrochloride)

Effective in hypertension, mild to severe

Catapres is distinguished by its broad clinical usefulness in the treatment of hypertension.

More than 600 major published papers*

The extensive experimental and clinical work with Catapres has been reported in hundreds of papers published in scientific journals in this country and abroad. Controlled studies[1-7] plus numerous other clinical evaluations have demonstrated that Catapres is an effective antihypertensive drug with these desirable properties:

does not alter normal hemodynamic responses to exercise

renal blood flow and glomerular filtration rate essentially unchanged

antihypertensive response enhanced by diuretics such as chlorthalidone

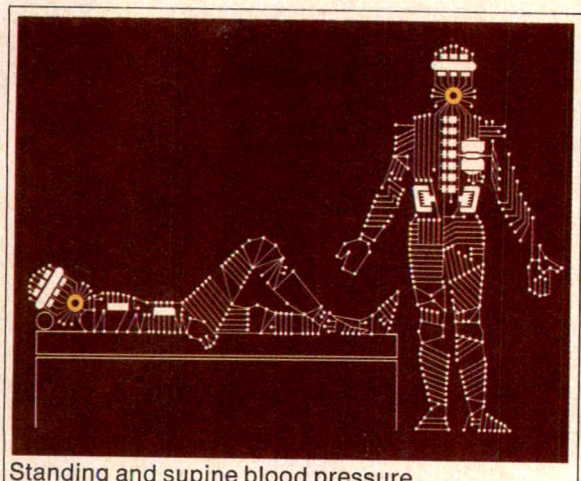
compatible with other antihypertensive agents

has been shown to reduce plasma renin activity and to decrease excretion of aldosterone and catecholamines
(See ACTIONS section of Brief Summary)

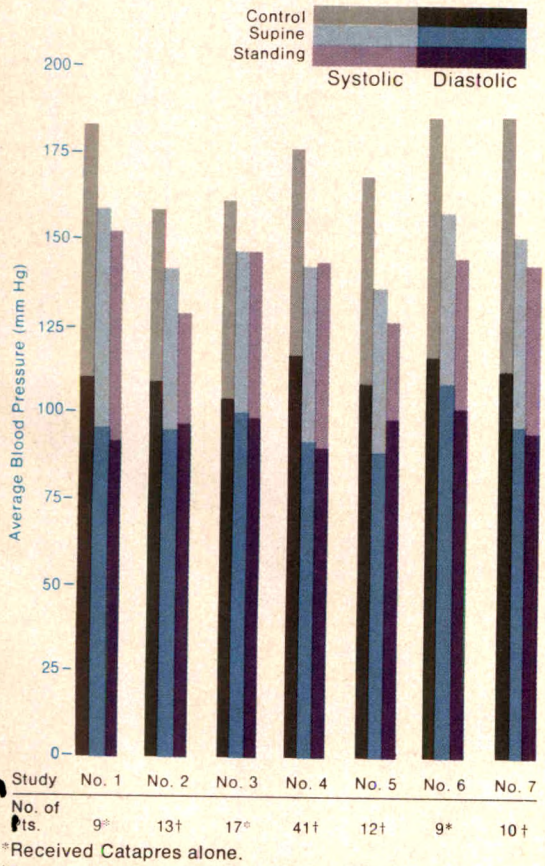
What to watch for—The principal side effects of Catapres are dry mouth, sedation, and drowsiness. Constipation, dizziness, headache, and fatigue also have been reported. Generally, these effects tend to diminish with continued therapy. As with other antihypertensive agents, tolerance may develop in some instances. For a more detailed discussion of side effects, warnings, and precautions, see the brief summary of prescribing information on the last page of this advertisement or consult the Catapres package insert.

*Complete Catapres bibliography available on request.

Mild and infrequent orthostatic effects

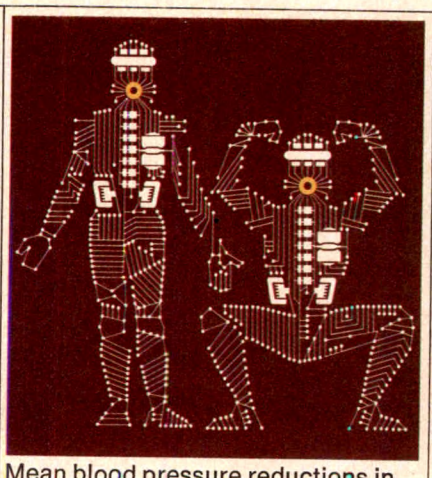


Standing and supine blood pressure response at the conclusion of therapy in 7 controlled studies[1-7]

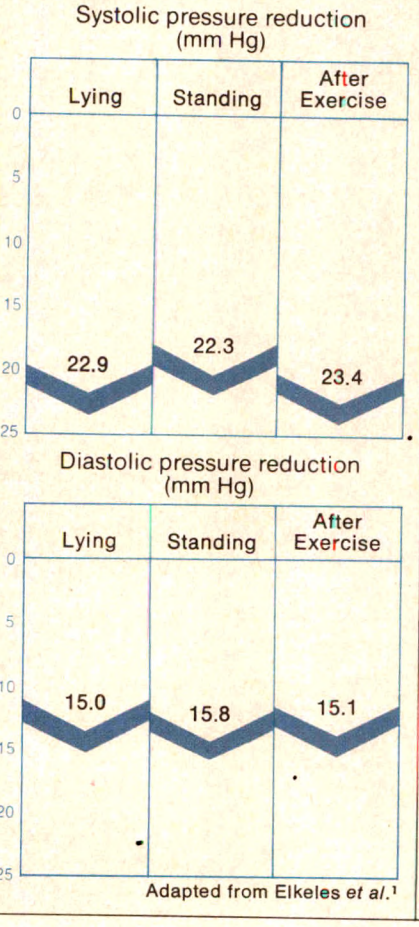


*Received Catapres alone.
†Received Catapres + a diuretic.
Note: In study No.4, blood pressure was taken in the sitting rather than the supine position.

Normal hemodynamic responses to exercise not altered

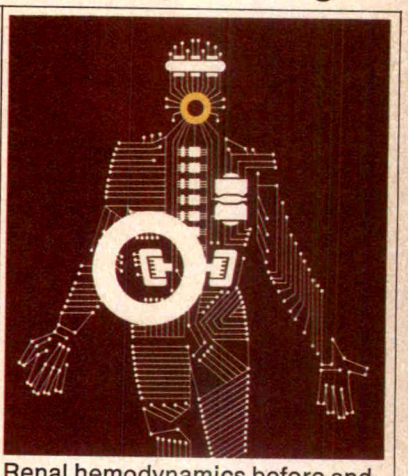


Mean blood pressure reductions in 9 hypertensive patients receiving Catapres (0.15 mg daily) for 4 weeks

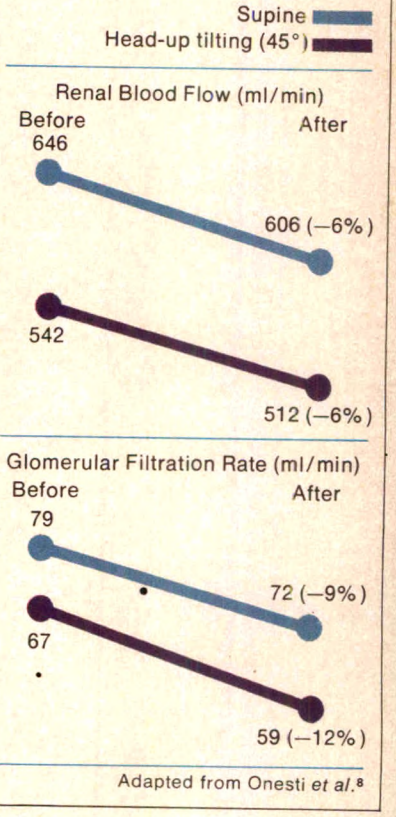


Adapted from Elkeles *et al.*[1]

Renal blood flow and glomerular filtration rate essentially unchanged

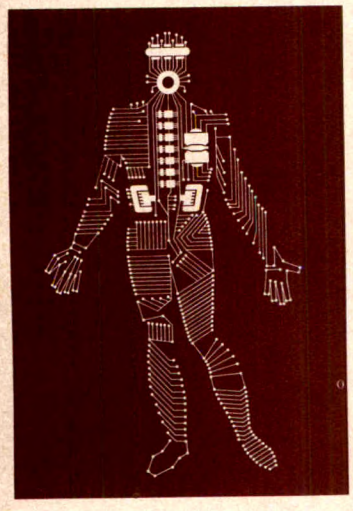


Renal hemodynamics before and after Catapres in 7 hypertensive patients. Mean blood pressure reductions were significant in both the supine position (from 155 to 128 mm Hg) and the standing position (from 151 to 101 mm Hg).



Adapted from Onesti *et al.*[8]

New from Boehringer Ingelheim



new Catapres®
(clonidine hydrochloride)

It's easy to start with Catapres. The usual starting dose of Catapres is one 0.1 mg tablet twice daily. Increments of 0.1 to 0.2 mg per day (up to the maximum daily dose of 2.4 mg) may be made until the desired blood pressure response is achieved.

How to stop Catapres. Reduce the dose gradually over two to four days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients on Catapres should be instructed not to discontinue therapy without consulting their physician. It has been demonstrated that a rapid rise in blood pressure, should it occur, can be reversed by resumption of Catapres or by administration of intravenous phentolamine.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Actions: The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic vasoconstrictor centers, thereby decreasing sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.
Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

References: 1. Elkeles, R. S., Goldby, F. S. and Oliver, D. O.: A Double Blind Study of Catapres, A New Hypotensive Agent, *in* Conolly, M. E. (ed.): Catapres in Hypertension, London, Butterworths, 1970, pp. 139-144. 2. Freis, E. D.: Data on file at Boehringer Ingelheim Ltd. 3. Hickler, R. B.: Data on file at Boehringer Ingelheim Ltd. 4. Mroczek, W. J., Leibel, B. A. and Finnerty, F. A., Jr.: Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic, Am. J. Cardiol. **29**:712, 1972. 5. Putzeys, M. R. and Hoobler, S. W.: Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients, Am. Heart J. **83**:464, 1972. 6. MacDonald, R. H. and Shapiro, A.: Data on file at Boehringer Ingelheim Ltd. 7. Kirkendall, W. M., Toubes, D. B. *et al.*: Hypertensive effects of clonidine and chlorthalidone, Am. Heart J. **82**:312, 1971. 8. Onesti, G. *et al.*: Pharmacodynamic effects of a new antihypertensive drug, Catapres (ST-155), Circulation **39**:219, 1969.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, New York 10523

The patient with cardiac arrhythmia may need medication most when he's least likely to take it...

while he's sleeping.

Quinaglute® Dura-Tabs® (quinidine gluconate)

- produces sustained serum quinidine levels, thus providing a convenient 8 or 12 hour dosage schedule
- usually insures uninterrupted therapeutic quinidine gluconate levels during sleep
- avoids peaks and valleys in plasma levels during which time the arrhythmias may recur
- maintains normal sinus rhythm following conversion by other techniques
- well tolerated to enhance patient cooperation — few G.I. disturbances

Contraindications: Quinaglute Dura-Tabs are contraindicated in patients with partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening; in patients manifesting idiosyncrasy or sensitivity to quinidine (e.g. febrile reactions, skin eruptions, thrombocytopenia, etc.), in patients with renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. It may be contraindicated in certain patients who have marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

Before prescribing or administering, please refer to QUINAGLUTE full product information.

Cooper Laboratories, Inc.
Wayne, New Jersey 07470

Quinaglute® Dura-Tabs®

(quinidine gluconate) 5 gr. (0.33 Gm.)

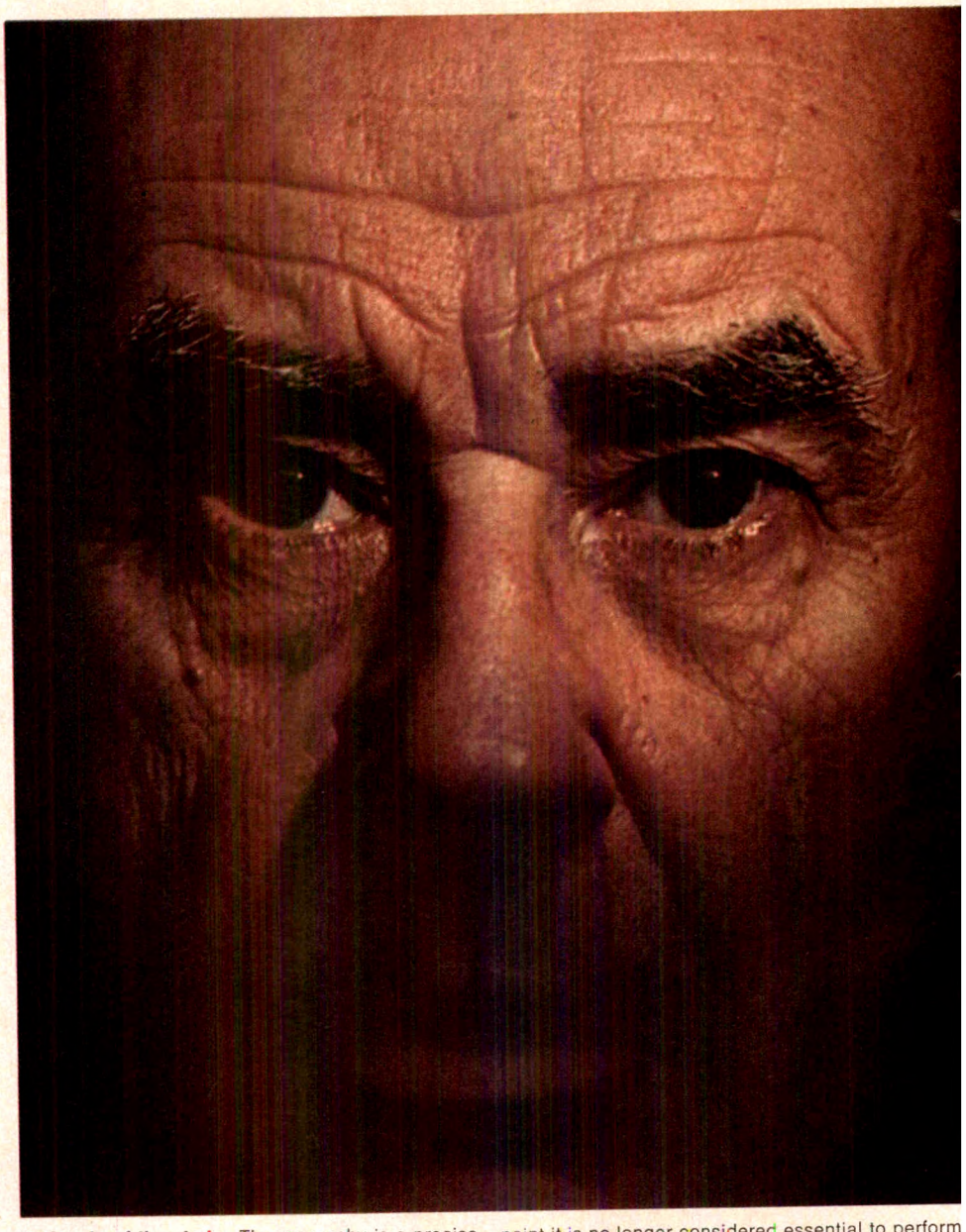
to help maintain the patient all through the night

101-37 44-4

How do you know a vasodilator works?

This thermographic study offers objective evidence of circulatory improvement.

Heretofore, subjective evaluations have cast doubt on the efficacy of cerebral vasodilators in increasing blood flow. Now, for the first time, thermography furnishes *objective* evidence of the case for Cerespan® (papaverine HCl): in a series of 9 patients, an "increase in cerebral blood flow due to the direct vasodilating effect of Cerespan (papaverine hydrochloride)."[1]



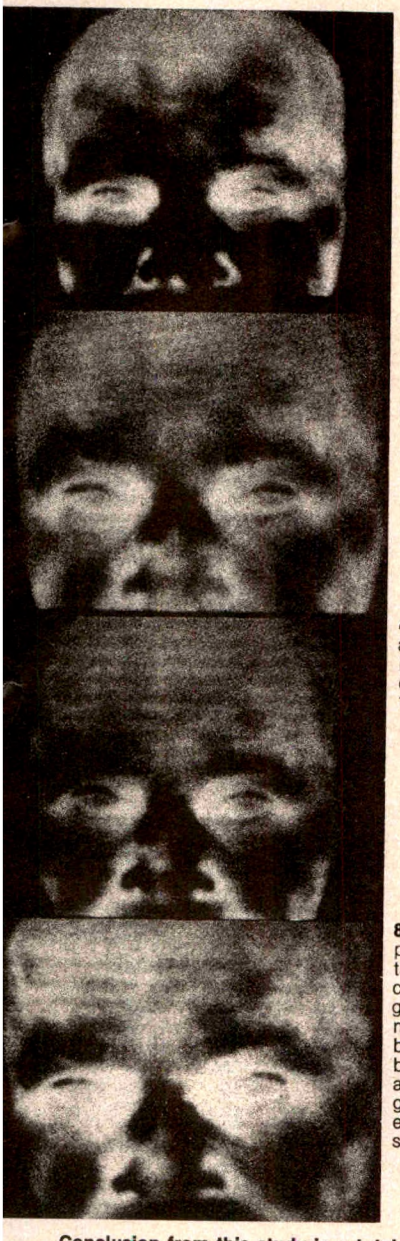
This photograph of a professional model illustrates the supraorbital and frontal areas studied thermographically in this investigation.

Rationale of the study—Thermography is a precise, simple means of measuring surface temperature. In a selected area of the body it can be used to estimate changes in blood flow by measuring the associated temperature changes.[2] It is not used for the assessment of cerebral function.

Unlike angiography, thermography is atraumatic and noninvasive.[1,2] A high degree of correlation between thermographic and angiographic studies in cerebral vessels has been observed. In evaluating the results of endarterectomy at the Neurological Institute of New York, the two techniques agreed in 95% of 119 patients.[3] "From the practical standpoint it is no longer considered essential to perform angiography if the thermogram reverts to normal."[3]

The supraorbital and frontal areas of the face were chosen for the Cerespan (papaverine HCl) study because they are perfused by branches of the ophthalmic artery, which in turn arises from the internal carotid artery. Changes in flow through the internal carotid artery, which perfuses the brain via the circle of Willis, produce corresponding changes in flow in the ophthalmic branch. These changes are detectable thermographically in the supraorbital and frontal areas.[4]

A CASE IN POINT: 8-HOUR IMPROVEMENT IN BLOOD FLOW



Control thermogram of 75-year-old male with arteriosclerotic heart disease shows severe supraorbital cooling on right, marked supraorbital and frontal cooling on left, indicating diminished blood flow to these areas supplied by branches of ophthalmic artery.

1 hour after administration of 300 mg. (2 capsules) of Cerespan, the thermogram shows very significant improvement: slight supraorbital cooling on right, slight supraorbital and frontal cooling on left.

4 hours after Cerespan was administered, improvement is maintained, no significant change is shown from 1-hour thermogram.

8 hours after Cerespan, improvement is still maintained, with no significant change from 1-hour thermogram. **Evaluation:** "very significant" improvement in blood flow to ophthalmic branch of internal carotid artery, evaluated thermographically, lasting for the entire 8-hour period of observation.

Conclusion from this study in a total of 9 patients: "These improvements in the thermograms were attributed to an increase in cerebral blood flow due to the direct vasodilating effect of Cerespan (papaverine hydrochloride)."[1]

When a vasodilato
is indicated,
there's a good case
for prescribing

Cerespar

(papaverine HCl) c

150 mg. in micro-dialysis cel

TO HELP INCREASE BLOOD FLOW TO

in transient ischemic attacks due to

relaxes vasospasm, thus provides vasc
on responsive cerebral blood v

helps decrease vascular resist

**WITH SIMPLE DOSAGE SCHEDULE TO
ADHERENCE TO YOUR THERAPEUTI**

q. 12 h. dosage provides uninterrupte
release around the clock

easier for the patient to remember ar
maximum benefit

if required, dosage may be increa
two capsules q. 12 h.

COMPLETE DETAILS ON THERMOGRAPHIC ST
CERESPAN® (papaverine HCl)

For full information on the studies described he
USV Representative or write to: Medical Services,
ceutical Corp., Tuckahoe, N.Y. 10707.

BRIEF SUMMARY Each Cerespan capsule conta
HCl 150 mg. in micro-dialysis cells. **Indications an**
relief of cerebral and peripheral ischemia associat
spasm, 1 capsule q. 12 h. **Precautions:** Use with
coma. Discontinue drug if hepatic hypersensitivit
testinal symptoms, jaundice, eosinophilia and altere
tests occur. **Adverse Reactions:** Anorexia, nausea,
tress, constipation or diarrhea, skin rash, malaise, d
tigo, sweating and headache. **Supplied:** Bottles o
drums of 5000; single-dose blister packs, boxes of 5

References: 1. Data on file, Department of Medical
Pharmaceutical Corp. 2. Karpman, H. L., Kalb, I. M.
J. J.: Geriatrics 27:96, 1972. 3. Wood, E. H. and Hila
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T. D. and Gumnit, R. J.: Stroke 4:57, 1973.

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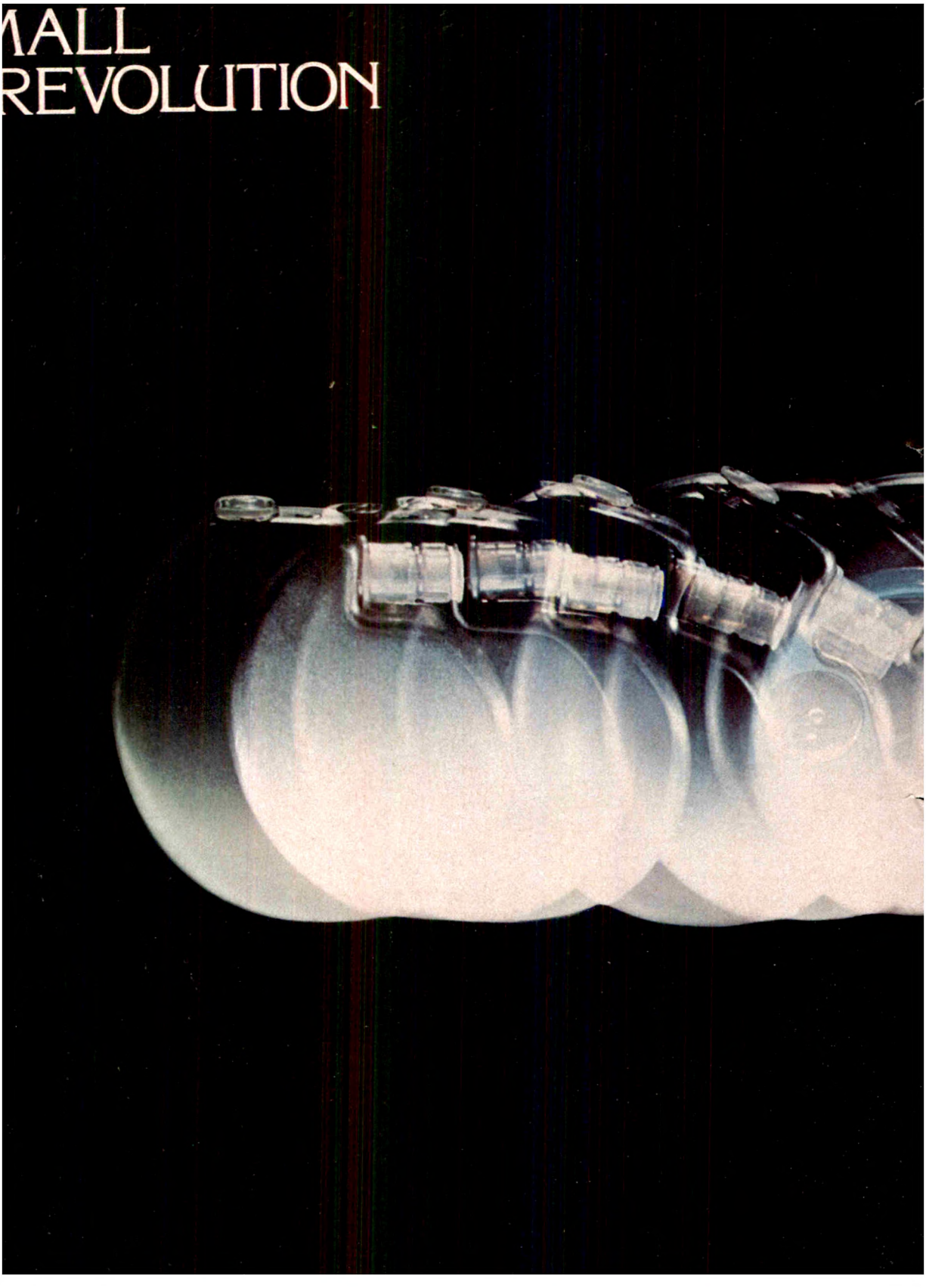
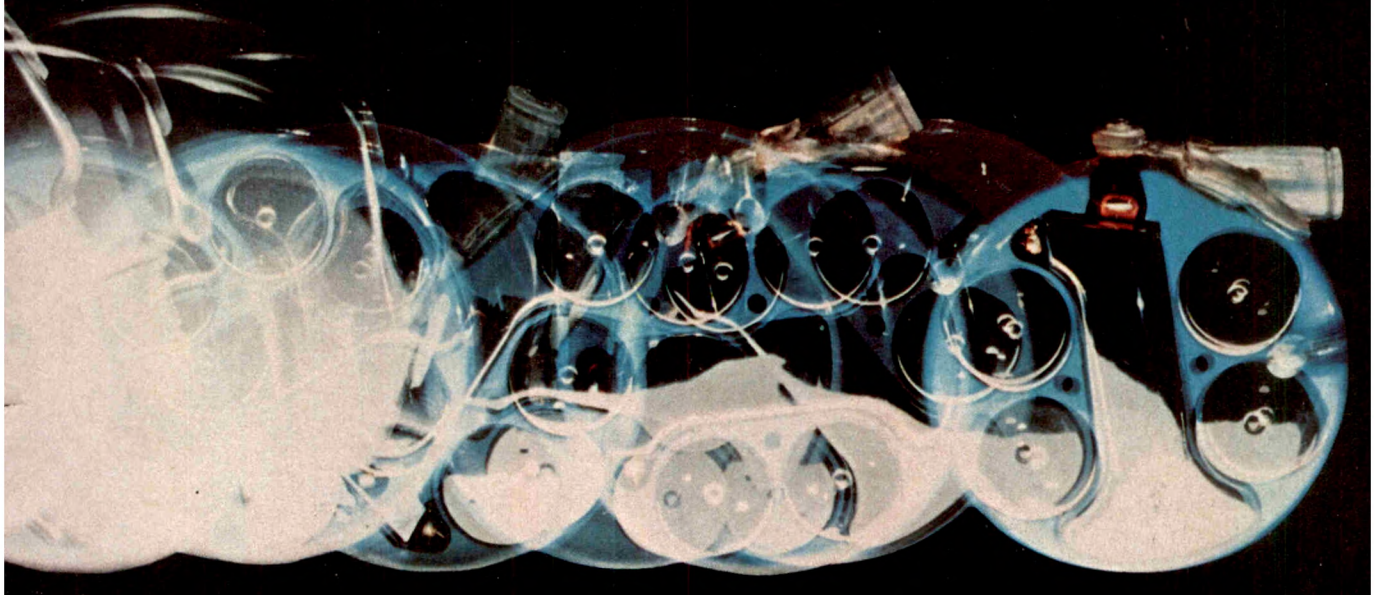

MALL
REVOLUTION

The New XYTRON™ Pulse Generator

It's a revolution, alright. Revolutionary in its smallness (illustration is actual size). And revolutionary in the fact that bipolar and unipolar models are now the same size.

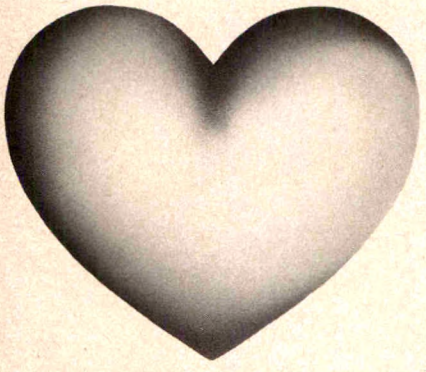
The XYTRON™ pulse generator is evolutionary, too. It features the familiar quality, reliability and performance characteristics that today make Medtronic the pacemaker of choice throughout the world. With advantages like Energy Conservation and Energy Compensation. Plus the proven double-barrier power cell.

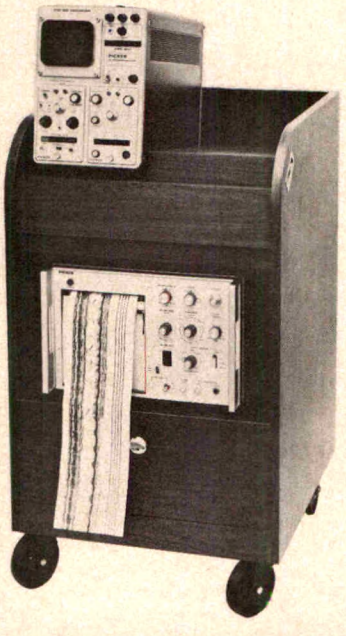


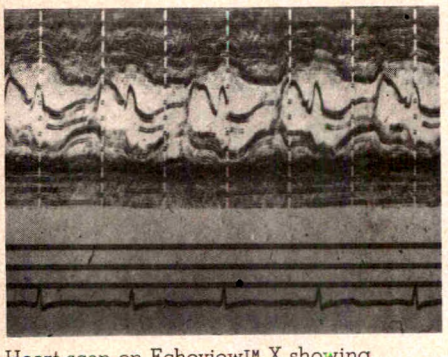
XYTRON™. A small revolution. The next logical step forward in pacemaking.

Medtronic maintains a worldwide network of offices and representatives to serve the medical profession. Check your local telephone directory.

Ultrasound. Who needs it?







Heart scan on Echoview™ X showing prolapsing mitral valve. Photo courtesy Dr. Fred Winsberg, Montreal General Hospital, Montreal, Quebec.

You do. And your patients do. For ultrasound is opening new vistas in diagnostic visualization. In fact, it's the fastest-growing of the more important imaging technics. (We know because we also make the other major types—both radioisotope and x-ray imaging systems.)

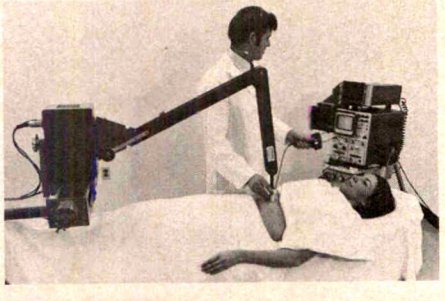
But why Picker ultrasound? A fair question to which there are several good and valid answers.

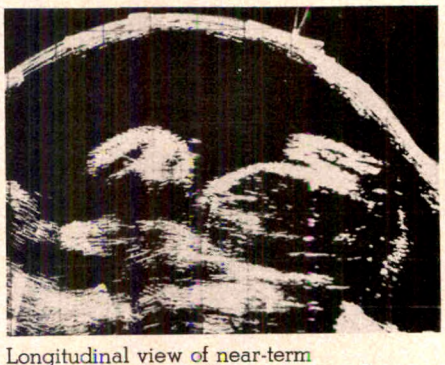
1. Picker has been the pioneer and leader since we introduced ultrasound equipment in this country a decade ago.
2. Picker equipment has stood the test of time. Picker continues in its leadership role by innovative design and thorough field testing. In fact, more ultrasound scans are made with Picker equipment than with all other scanners combined.
3. Picker's new cardiac unit extends the breadth of our equipment line to encompass virtually every ultrasound requirement.
4. Picker systems are modularized and upgradable. And being American-made, that means you get all the improvements first since systems responsibility is right here.
5. Picker puts the clincher on with the largest field technical-service force in the industry. You get right-now Picker service by Picker personnel. No third parties are involved.

For a sound diagnosis, rely on Picker ultrasound. It's an ultrasound buying decision, too.

See your local Picker representative. Or contact Picker Corporation, 595 Miner Road, Cleveland, OH 44143.

PICKER®
ONE OF THE C.I.T. COMPANIES





Longitudinal view of near-term anencephalic fetus. Photo courtesy Dr. George Leopold, University of California, San Diego, California.

IN ANGINA*: **ACTS WITH SUBLINGUAL SPEED**

CHEWABLE SORBITRATE® 5MG.
ISOSORBIDE DINITRATE

As with sublingual ISDN:
acts in 2 minutes for therapeutic use...
acts up to 2 hours for prophylaxis.

In addition:
chewing action helps distribute nitrate over a larger mucosal area.

SUMMARY OF
PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.
Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.
Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.
Dosage and Administration: Route: Sublingual, oral and chewable tablets.
Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:
Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.
Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.
It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, Delaware 19897

Now...
NIPRIDE™ (sodium nitroprusside)
Immediate, predictable control

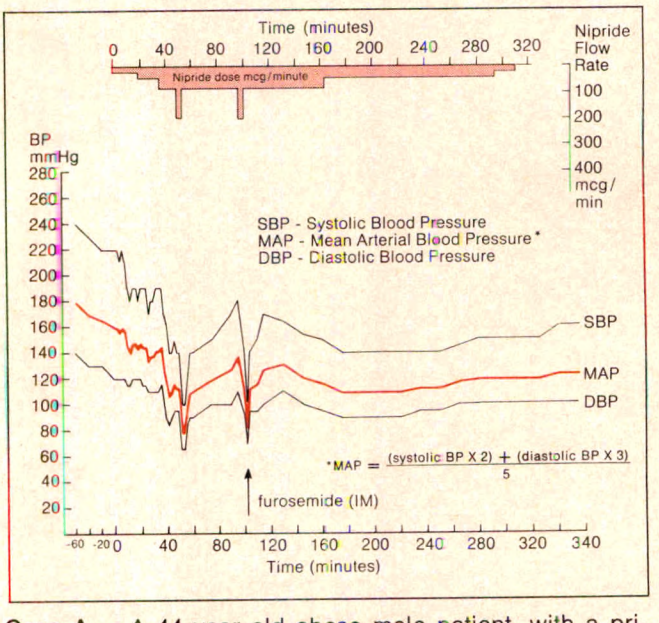
When immediate steps must be taken to lower excessive blood pressure, Nipride (sodium nitroprusside) is a potent antihypertensive agent that acts by direct peripheral vasodilatation, accompanied by reduction of total calculated peripheral vascular resistance.

WORKS IMMEDIATELY. Nipride's antihypertensive effect may be seen within seconds after the beginning of intravenous infusion.

SHORT-ACTING. On cessation of Nipride administration, blood pressure will begin to rise within seconds to reach pretreatment levels in one to ten minutes. Thus, with careful monitoring and titration of Nipride dosage, the physician may reduce the patient's blood pressure as rapidly as he deems advisable, stabilize it at the desired level, sustain that level for hours — a few days if necessary — or until slower-acting medications become effective. Administration of oral antihypertensive medication should be started early in the course of treatment and Nipride dosage reduced accordingly as blood pressure begins stabilizing at desired levels. With frequent monitoring, hypotensive episodes may be avoided since Nipride permits minute-to-minute control of the patient's blood pressure.

Side Effects — reported side effects, such as nausea, retching, diaphoresis, etc., are probably related to excessively rapid lowering of blood pressure. *Contraindications* — compensatory hypertension, *e.g.*, arteriovenous shunt or coarctation of the aorta. *Compatibilities* — oral antihypertensive medications may be administered simultaneously with frequent monitoring to observe their additive effects. *Response* — consistent hypotensive effect regardless of patients' resistance to other antihypertensive medications. Reports of tachyphylaxis have been rare.

DOSAGE MUST BE INDIVIDUALIZED. Patient response varies widely over a range of 0.5 mcg/kg/min to 8.0 mcg/kg/min. It is evident, therefore, that infusion rates should be started at a minimal level, patient response observed for a few minutes, then dosage increased by a measured



Case A — A 44-year-old obese male patient, with a primary diagnosis of essential hypertension, was admitted to a hospital with impending hypertensive encephalopathy. An infusion of Nipride (sodium nitroprusside) was started at approximately 25 mcg/min and then slowly increased to a dosage of 80 mcg/min during the first 40 minutes of administration. Dosage increase to 200 mcg/min at 50 minutes and 100 minutes resulted in sharp drops in blood pressure. As soon as the infusion was reduced to 80 mcg/min, there was an immediate rise in pressure to approximate levels previously observed with the same dosage. During Nipride administration, a single 40 mg IM dose of furosemide was given at approximately 100 minutes. The patient was subsequently maintained on oral medication (furosemide 40 mg, q.i.d., and triamterene 100 mg, q.i.d.).

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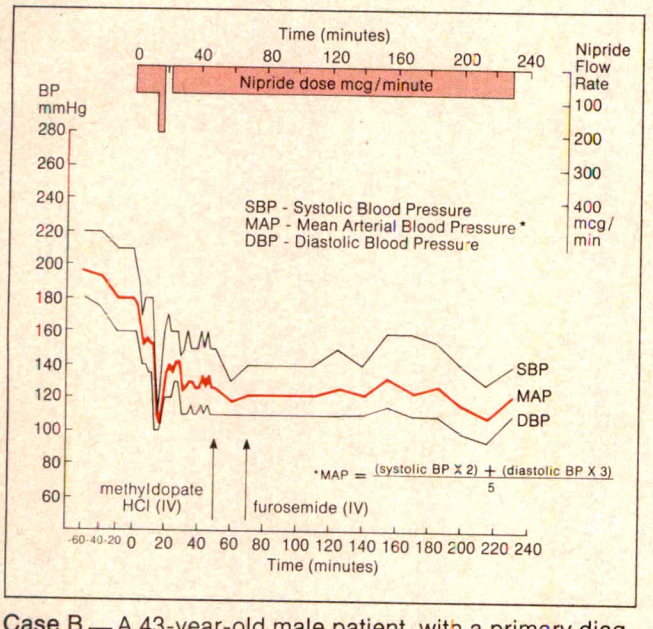
for IV infusion.
in hypertensive crises.

increment and the process continued until blood pressure has reached a desired level. As examples of the procedure, Case A responded slowly, requiring increasing dosage increments; Case B responded rapidly, calling for a brief discontinuation of the infusion.

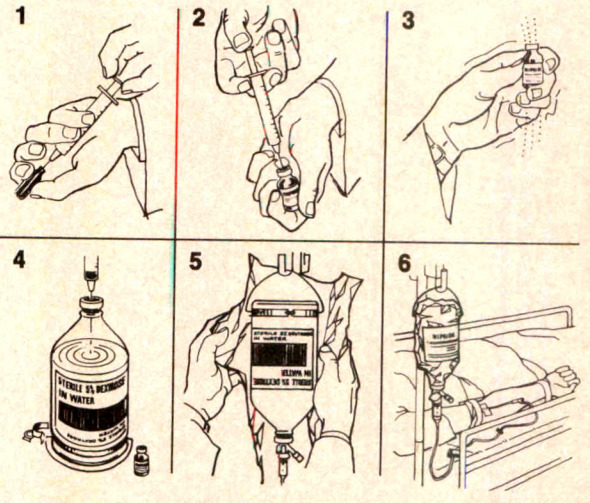


Case B — A 43-year-old male patient, with a primary diagnosis of essential hypertension and secondary diagnoses of impending left ventricular failure, headache and renal failure, was admitted to a hospital in hypertensive crisis. Nipride (sodium nitroprusside) infusion was started at 100 mcg/min, which produced a relatively small decrease in pressure. Infusion rate was then doubled, resulting in a sharp drop in blood pressure. Infusion was stopped for ten minutes until blood pressure rose, then resumed at the 100 mcg/min rate, which maintained pressure at a satisfactory level. Preliminary to discontinuation of Nipride, methyldopate HCl (500 mg IV) and furosemide (80 mg IV) were administered in single intravenous doses at 50 and 70 minutes respectively. The patient was subsequently maintained on oral medication (methyldopa 500 mg, q.i.d., and furosemide 40 mg, q.i.d.).

NIPRIDE MIXING PROCEDURE

FOR INTRAVENOUS INFUSION USE ONLY.
DO NOT ADMINISTER BY DIRECT INJECTION.

Nipride must be prepared immediately before administration. Once prepared, solutions containing Nipride should not be kept or used longer than four hours. No other medication should be added to the solution.



1. Withdraw 2 to 3 ml of sterile dextrose in water only. Any commercially available sterile dextrose in water in ampul form may be used. **2.** Aseptically add the dextrose in water to the 50-mg Nipride vial. **3.** Gently agitate to completely dissolve powder. **4.** Add all of the reconstituted solution to 500 or 1000 ml of sterile 5 percent dextrose in water depending on desired concentration. **5.** Promptly wrap Nipride solution in aluminum foil or other opaque material to protect from light. **6.** Administer prepared solution by infusion pump, micro-drip regulator or any similar device that will allow precise measurement of flow rate.

NIPRIDE™
(sodium nitroprusside)

50-mg vial

EMERGENCY BLOOD PRESSURE CONTROL

ROCHE

Please see following page for complete product information.

IN HYPERTENSIVE CRISES

EMERGENCY BLOOD PRESSURE CONTROL

NIPRIDE™
(sodium nitroprusside)

Nipride is only to be used as an infusion with sterile 5% dextrose in water. Not for direct injection.

DESCRIPTION: Nipride (sodium nitroprusside) in injectable form contains the equivalent of 50 mg of sodium nitroprusside dihydrate (sodium nitrosylpentacyanoferrate [III]) in a 5-ml amber-colored, rubber-stoppered vial. Chemically, sodium nitroprusside is $Na_2Fe(CN)_5NO{\cdot}2H_2O$. Nipride is a reddish-brown powder which is soluble in water. In aqueous solution, it is photosensitive and should be protected from light.

ACTIONS: Nipride is a potent, rapid acting, intravenous antihypertensive agent. This action is probably due to the nitroso (NO) group. Its effect is almost immediate and ends when the IV infusion is stopped. The brief duration of the drug's action is due to its rapid conversion to thiocyanate. The hypotensive effect is augmented by ganglionic blocking agents.

The hypotensive effects of Nipride are caused by peripheral vasodilatation as a result of a direct action on the blood vessels, independent of autonomic innervation. No relaxation is seen in the smooth muscle of the uterus or duodenum *in situ* in animals.

INDICATIONS: Nipride is indicated for the immediate reduction of blood pressure of patients in hypertensive crises. Concomitant oral antihypertensive medication should be started while the hypertensive emergency is being brought under control with Nipride. There is no contraindication in using Nipride simultaneously with oral antihypertensive medications.

CONTRAINDICATIONS: Nipride should not be used in the treatment of compensatory hypertension, *e.g.,* arteriovenous shunt or coarctation of the aorta.

WARNINGS: Nipride is only to be used as an infusion with sterile 5% dextrose in water. Not for direct injection.

Since an end product of Nipride metabolism, thiocyanate, inhibits both the uptake and binding of iodine, caution should be exercised in using Nipride in patients with hypothyroidism or severe renal impairment.

Blood levels of thiocyanate should be determined if treatment is to be extended in patients with severe renal dysfunction. Although intravenous infusions of Nipride are not intended for long-term use, as long as blood thiocyanate levels are measured daily and do not exceed 10 mg/100 ml, it is probably safe to continue with the infusion until the patient can be safely treated with oral antihypertensive medications.

Hypertensive patients are more sensitive to the intravenous effect of sodium nitroprusside than are normotensive subjects. Patients who are receiving concomitant antihypertensive medications are more sensitive to the hypotensive effect of sodium nitroprusside and the dosage of Nipride should be adjusted accordingly.

Usage in Pregnancy: The safety of Nipride in women who are or who may become pregnant has not been established; hence, it should be given only when the potential benefits have been weighed against possible hazard to mother and child.

Usage in Children: The safety of Nipride in children has not been established. Clinical experience is limited. Further studies are in progress to determine its proper dosage and administration.

PRECAUTIONS: Adequate facilities, equipment and personnel should be available for frequent and vigilant monitoring of blood pressure, since the hypotensive effect of Nipride (sodium nitroprusside) occurs rapidly. When the infusion is slowed or stopped, blood pressure usually begins to rise immediately and returns to pretreatment levels within one to ten minutes. It should be used with caution and initially in low doses in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

Because of the rapid onset of action and potency of Nipride, it should preferably be administered with the use of an infusion pump, micro-drip regulator, or any similar device that would allow precise measurement of the flow rate.

Once dissolved in solution, Nipride tends to deteriorate in the presence of light. Therefore, it should be protected from light by wrapping the container of the prepared solution with aluminum foil or other opaque materials. Solutions of Nipride should not be kept or used longer than four hours.

Nipride in aqueous solution yields the nitroprusside ion which reacts with even minute quantities of a wide variety of inorganic and organic substances to form usually highly colored reaction products (blue, green or dark red). If this occurs the infusion should be replaced.

ADVERSE REACTIONS: Nausea, retching, diaphoresis, apprehension, headache, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain have been noted with too rapid reduction in blood pressure, but these symptoms rapidly disappeared with slowing of the rate of the infusion or temporary discontinuation of infusion and did not reappear with continued slower rate of administration.

One case of hypothyroidism following prolonged therapy with intravenous sodium nitroprusside has been reported. A patient with severe hypertension with uremia received 3900 mg of sodium nitroprusside intravenously over a period of 21 days. This is one of the longest reported intravenous uses of this agent. There was no tachyphylaxis, but the patient developed evidence of hypothyroidism, together with retention of thiocyanate (9.5 mg/100 ml). With peritoneal dialysis the thiocyanate level diminished and the signs of hypothyroidism subsided.

DOSAGE AND ADMINISTRATION: The contents of a 50-mg Nipride vial should be dissolved in 2 to 3 ml of dextrose in water. No other diluent should be used. Depending on the desired concentration, all of the prepared stock solution should be diluted in 500 to 1000 ml of 5 percent dextrose in water and promptly wrapped in aluminum foil or other opaque materials to protect from light. Both the stock solution and the infusion solution should be freshly prepared and any unused portion discarded. The freshly prepared solution for infusion has a very faint brownish tint. If it is highly colored, it should be discarded (see PRECAUTIONS). *Once prepared, the solution should not be kept or used longer than four hours. The infusion fluid used for the administration of Nipride should not be employed as a vehicle for simultaneous administration of any other drug.*

In patients who are not receiving antihypertensive drugs, the average dose of Nipride is 3 μg/kg/minute (range of 0.5 to 8 μg/kg/minute). Usually, an average of 200 μg/minute (range of 20 to 400 μg/minute) is sufficient to maintain the blood pressure at 30 to 40 percent lower than the pretreatment diastolic blood pressure levels. In hypertensive patients receiving concomitant antihypertensive medications, smaller doses are required. In order to avoid excessive levels of thiocyanate and lessen the possibility of a precipitous drop in blood pressure, the maximum recommended dose is 800 μg/minute.

1 Vial (50 mg) Nipride (sodium nitroprusside) in 500 ml 5% DW (100 μg/ml)

Dose/kg	μg/kg/min	ml/kg/min
Average	3	0.03
Range	0.5 to 8	0.005 to 0.08
Dose for a 70 kg patient	**μg/70 kg/min**	**ml/70 kg/min**
Average	200	2.0
Range	35 to 560	0.35 to 5.6

The intravenous infusion of Nipride should be administered by an infusion pump, micro-drip regulator or any similar device that will allow precise measurement of the flow rate. Care should be taken to avoid extravasation. The rate of administration should be adjusted to maintain the desired antihypertensive effect, as determined by frequent blood pressure determinations. Nipride infusion may be continued until the patient can safely be treated with oral antihypertensive medications alone.

HOW SUPPLIED: Nipride injectable is supplied in 5-ml amber-colored vials containing the equivalent of 50 mg sodium nitroprusside dihydrate for reconstitution with dextrose in water (available singly and in packages of 10).

HUMAN PHARMACOLOGY: Sodium nitroprusside administered intravenously to hypertensive and normotensive patients produced a marked lowering of the arterial blood pressure, slight increase in heart rate, a mild decrease in cardiac output and a moderate diminution in calculated total peripheral vascular resistance.

The decrease in calculated total peripheral vascular resistance suggests arteriolar vasodilatation. The decreases in cardiac and stroke index noted may be due to the peripheral vascular pooling of blood.

In hypertensive patients, moderate depressor doses induce renal vasodilatation roughly equivalent to the decrease in pressure without an appreciable increase in renal blood flow or a decrease in glomerular filtration.

In normotensive subjects, acute reduction of mean arterial pressure to 60 to 75 mm Hg by infusion of sodium nitroprusside caused significant increase in renin activity of renal venous plasma in correlation with a degree of reduction in pressure. Renal response to reduction in pressure was more striking in renovascular hypertensive patients, with significant increase in renin release occurring from the involved kidney at mean arterial pressures ranging from 90 to 137 mm Hg. Furthermore, the magnitude of renin release from the involved kidney was significantly greater when compared with that in normotensive subjects, while in the contralateral, uninvolved kidney, no significant release of renin was detected during the reduction of pressure.

THIS PRODUCT INFORMATION ISSUED JULY 1974

For a copy of the comprehensive Nipride Monograph, please write to Professional Services Department, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, New Jersey 07110

Unique long-acting nitrate formulation.. proved in years of practice

Nitrol® Nitroglycerin Ointment 2%

1955 "Because of the ineffectiveness of the conventional measures, it was suggested that a 2% nitroglycerin ointment [Nitrol] be applied to the skin....It is the authors' impression that there has been definite benefit from this therapy, when used together with all other measures for the treatment of angina pectoris....The principle of slower absorption with resulting prolonged action of an effective coronary vasodilator would seem to deserve further trial in this condition."[1]

1974 "...nitroglycerin ointment [Nitrol] exhibited a consistently prolonged beneficial influence that, in practice, has never been demonstrated for any other nitrate used in the therapy of angina."[2]

Composition: Nitroglycerin 2% in lanolin-petrolatum base. **Administration:** From 1/2 to 2 inches applied to desired skin area by means of Appliruler supplied. Adjust to individual need, starting in lower range. **Side effects:** Headache indicates overdose. Dizziness on standing may be the result of postural hypotension. **Contraindications:** Marked anemia, increased intraocular pressure or increased intracranial pressure. **Supplied:** 1-oz. or 2-oz. tubes. **Caution:** Federal law prohibits dispensing without prescription.

References: 1. Davis, J. A., and Wiesel, B. H.: Am. J. Med. Sci. **230**:259-263 (Sept.) 1955. **2.** Reichek, N.; Goldstein, R. E.; Redwood, D. R., and Epstein, S. E.: Circulation **50**:348-352 (August) 1974.

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Lanoxin
[digoxin]
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precision quality control...
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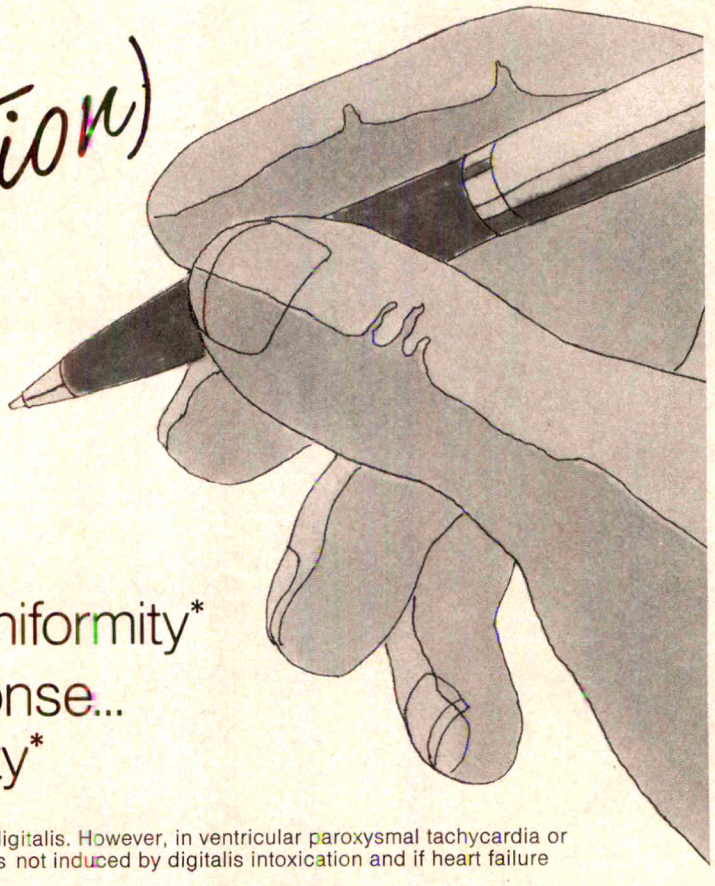

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

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JANUARY 1975

The American Journal of CARDIOLOGY®

VOLUME 35

NUMBER 1

CLINICAL STUDIES

Left Ventricular Function in Patients With and Without Myocardial Infarction and One, Two or Three Vessel Coronary Artery Disease

ROGER E. MORASKI, MD
RICHARD O. RUSSELL, Jr., MD, FACC
McKAMY SMITH, MD, PhD
CHARLES E. RACKLEY, MD, FACC

Birmingham, Alabama

Ninety-six patients with chest pain were studied to determine the relation between left ventricular function and severity of coronary artery disease in patients with and without a history of myocardial infarction. Coronary arteriography was performed obtaining cineangiograms (60 frames/sec) and large roll film angiograms (2 to 6 frames/sec) for precise definition of the coronary anatomy. The criteria for diagnosis of myocardial infarction were a typical history, a rise and fall in serum glutamic oxaloacetic transaminase levels and evolutionary S-T segment changes associated with Q waves of at least 0.03 second. Left ventricular function was assessed by measurement of left ventricular end-diastolic pressure and volume, and left ventricular ejection fraction, mass and compliance. Fifteen patients had normal findings; 81 were classified according to number of diseased vessels and presence or absence of myocardial infarction. There were no group differences in age or heart rate. Left ventricular end-diastolic pressure was abnormally increased in patients with three vessel disease and myocardial infarction. Left ventricular end-diastolic volume was increased and the ejection fraction was reduced in patients in each vessel disease group with myocardial infarction. Although ejection fraction was reduced in patients with three vessel disease without myocardial infarction, it was further reduced when infarction occurred. Left ventricular mass increased in patients with three vessel disease with or without myocardial infarction. Values for ventricular compliance were reduced in all patients with myocardial infarction and were lower in those with two and three vessel disease and infarction than in those with two and three vessel disease without infarction. These findings suggest that a previous history of myocardial infarction needs to be considered together with anatomic abnormalities of the coronary arteries in assessing cardiac performance in patients with ischemic heart disease. In patients with one, two or three vessel coronary artery disease, a previous myocardial infarction significantly alters left ventricular performance; the ejection fraction is a more sensitive measurement of left ventricular function than left ventricular end-diastolic pressure or volume.

From the Department of Medicine, University of Alabama Medical Center, Birmingham, Ala. This study was supported by Myocardial Infarction Research Unit Contract PH43-67-1441 and Cardiovascular Research and Training Center Program Project Grant HE 11,310 from the National Institutes of Health, Bethesda, Md., and Clinical Research Center Grant 5MO1 RROOO 32-13, Department of Health Education and Welfare, Bethesda, Md.

Address for reprints: Roger E. Moraski, MD, Department of Medicine, University of Alabama Medical Center, University Station, Birmingham, Ala. 35294.

Recent epidemiologic reports indicate that survival of patients with angiographically proved occlusive coronary artery disease depends on (1) the extent of atherosclerotic involvement of the coronary arteries,[1–3] (2) the presence of a scar of myocardial infarction, [2,4] and (3) the severity of left ventricular dysfunction.[2,4]

The direct relation between mortality and the number of coronary arteries with obstructive or stenotic lesions, or both, makes it imperative to define the pathologic anatomy of the coronary arteries in patients with chest pain. This definition is even more important if the patient has a history or electrocardiographic changes consistent with myocardial infarction since mortality is significantly increased in patients with prior infarction. Left ventricular dysfunction demonstrated clinically or by left ventricular angiography further increases mortality even among patients with single vessel disease. Finally, the availability of saphenous vein bypass surgery in the treatment of angina pectoris and ischemic heart disease demands precise evaluation of coronary anatomy and left ventricular function for optimal patient selection.[5–8] Accordingly, the purpose of this study was to characterize and compare left ventricular function among groups of patients with one, two or three vessel coronary artery disease and, within these groups, to analyze differences in ventricular function among patients with and without previous infarction.

Methods

After receiving an explanation of the procedure and giving consent, 96 patients, 77 male and 19 female, referred for evaluation of chest pain underwent complete clinical and hemodynamic study by cardiac catheterization. The ages of the patients ranged from 33 to 67 years. One patient was studied before and after having sustained a myocardial infarction; thus, 97 studies are available for analysis. Patients were catheterized in the fasting state after premedication with intramuscular injection of diazepam (Valium®), 10 mg, and atropine sulfate, 0.6 mg.

Coronary arteriography was performed using Judkins' technique[9]; cineangiograms (60 frames/sec) and large roll film angiograms (2 to 6 frames/sec) in multiple views were obtained for evaluation of the coronary anatomy and allowed precise definition of the arterial lesions. Coronary lesions were considered significant if 50 percent or more of the luminal diameter was stenotic. Significant lesions in the left main, left anterior descending, left circumflex and right coronary arteries were classified in four groups: at least 50 percent stenosis; more than 50 to less than 90 percent stenosis; 90 percent or greater stenosis; and 100 percent occlusion. The first marginal branch of the circumflex artery and the posterior descending artery were considered continuations of major vessels since they supply large portions of ventricular muscle.

Left ventricular pressure was recorded before left ventricular angiography with use of fluid-filled catheters, a P23D pressure transducer and a multichannel recorder. Zero pressure reference was 10 cm above the table top. Special care was taken to optimize the frequency response of the pressure recording system.[10] The system was thoroughly flushed to remove visible air bubbles; a screw clamp damping valve containing a 4 cm length of semirigid Tygon tubing (internal diameter 1/16 inch, external diameter 1/18 inch) was used for "critical damping" of pressure recordings. The pressure transducer was connected to one end of this valve by a three-way stopcock so that a "square wave" signal could be produced by maintaining constant manual pressure on the syringe while rapidly turning this pressure into and out of the transducer with the stopcock. The screw on the valve was tightened until minimal "undershoot" appeared on the downstroke of the "square wave."

Left ventricular biplane angiograms were obtained at a rate of 6 or 12 frames/sec after left ventricular pressure injection of 50 to 60 ml of 76 percent sodium and meglumine diatrizoates using a technique previously described.[11] Ventricular volumes were calculated during sinus rhythm from biplane angiograms by the Dodge area-length method.[12,13] Films exposed during a premature ventricular contraction and the following beat were excluded from analysis. Left ventricular end-diastolic volume, left ventricular mass[14] and left ventricular ejection fraction (ratio of ventricular stroke volume to left ventricular end-diastolic volume) were calculated. Left ventricular compliance was calculated from the formula $LVC = (\Delta V/ESV)/\Delta P$, where LVC = left ventricular compliance; ΔV = the left ventricular volume change or the angiographic stroke volume calculated as the end-diastolic volume minus the end-systolic volume in milliliters; ESV = end-systolic volume used to calculate diastolic fractional volume change; and ΔP = the left ventricular diastolic pressure change calculated from the optimally damped system as the end-diastolic pressure minus the lowest early diastolic pressure and averaged for 8 to 12 cycles prior to left ventricular angiography.

The small segment of a pressure-volume curve between the lowest level of early diastolic pressure and end-diastolic pressure was considered to be linear and this assumption allowed approximations of left ventricular compliance among patients with and without infarction and various degrees of coronary artery disease.[15–17]

The criteria for diagnosis of a prior transmural myocardial infarction included a typical clinical history, abnormal rise and fall of serum glutamic oxaloacetic transaminase (SGOT) levels and evolutionary S-T segment changes of infarction associated with Q waves of 0.03 second or greater or Q-S complexes in at least 2 of the standard 12 electrocardiographic leads.

The criteria for prior myocardial infarction were met in 41 patients, 12 with one vessel, 12 with two vessel and 17 with three vessel disease. In 29 of the 41 patients the infarction had occurred less than 1 year and in 9 patients less than 2 years before the study; 3 patients had had their only infarction more than 2 years before the study. No patient had sustained more than one myocardial infarction. There were 17 anterior and 24 inferior wall myocardial infarctions. Forty-one patients had not had a myocardial infarction.

Results

Normal subjects: Fifteen of the 96 patients had normal coronary arteriograms, normal left ventricular function by the parameters measured and no history or electrocardiographic or serum enzyme changes consistent with myocardial infarction. These data (Table I) are in agreement with the data on normal left ventricular volume reported by Kennedy et al.[18] The remaining patients were classified on the basis of number of diseased vessels and the presence or absence of myocardial infarction.

TABLE I

Normal Data

Case no.	Age (yr) & Sex	HR	LVEDP	LVEDV	LV EF	LV Mass	LV Compliance
1	34M	80	8	77	0.55	98	0.14
2	55M	71	11	90	0.53	130	0.11
3	39M	91	10	72	0.51	83	0.12
4	43M	52	12	73	0.57	89	0.12
5	59M	67	12	75	0.64	105	0.11
6	53M	92	2	70	0.54	94	0.29
7	33M	70	8	87	0.52	71	0.22
8	44M	81	10	70	0.50	86	0.19
9	43M	90	5	75	0.53	104	0.13
10	45M	67	3	89	0.52	114	0.39
11	46F	81	3	56	0.59	77	0.23
12	33F	100	3	59	0.54	48	0.20
13	49F	111	10	66	0.58	63	0.23
14	54F	62	5	67	0.59	106	...
15	51F	61	8	39	0.60	109	0.31
Mean ± SD	45 ± 8	78 ± 16	7 ± 4	71 ± 13	0.55 ± 0.04	92 ± 21	0.20 ± 0.09

EF = ejection fraction; HR = heart rate (beats/min); LV = left ventricular; LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEDV = left ventricular end-diastolic volume (ml/m²); LV Mass = left ventricular mass (g/m²); SD = standard deviation.

TABLE II

Data in 23 Patients With One Vessel Disease

Case no.	Age (yr) & Sex	Coronary Stenosis	HR	LVEDP	LVEDV	LV EF	LV Mass (g/m²)	LV Compliance
		A. 11 Patients Without Myocardial Infarction						
1	48F	LAD: ≥90% prox 1/3	106	4	49	0.51	70	0.23
2	46F	LAD: ≥90% prox 1/3	79	11	68	0.58	77	0.18
3	52F	LAD: ≥90% prox 1/3	85	8	68	0.52	90	0.13
4	46F	LAD: ≥90% prox 1/3	86	4	63	0.47	79	0.19
5	55F	LAD: ≥90% prox 1/3	86	6	62	0.60	87	0.23
6	43F	LAD: ≥90% mid 1/3	86	5	62	0.52	85	0.14
7	49M	LAD: ≥90% mid 1/3	72	5	95	0.49	93	...
8	50M	LAD: >50-<90% prox 1/3	88	13	73	0.52	110	0.13
9	60M	LAD: >50-<90% prox 1/3	72	7	59	0.64	96	0.33
10	42M	LAD: >50-<90% prox 1/3	78	4	64	0.52	67	0.21
11	62M	RCA: 50% prox 1/3	67	23	77	0.61	106	0.12
Mean ± SD	50 ± 6		82 ± 11	8 ± 6	67 ± 12	0.54 ± 0.05	87 ± 14	0.19 ± 0.06
		B. 12 Patients With Myocardial Infarction						
12	56M	LAD: 100% prox 1/3	107	16	155	0.14	111	0.02
13	44M	LAD: ≥90% prox 1/3	57	7	72	0.30	94	0.02
14	57M	LAD: ≥90% prox 1/3	77	16	115	0.33	163	0.04
15	38M	LAD: >50-<90% prox 1/3	72	12	77	0.44	106	0.29
16	47M	LAD: >50-<90% prox 1/3	112	9	89	0.53	127	0.14
17	37F	LAD: ≥90% mid 1/3	108	11	62	0.35	83	0.14
18	38M	LAD: >50-<90% mid 1/3	67	13	111	0.40	122	0.06
19	47M	LCx: 100% prox 1/3	73	6	72	0.48	91	0.22
20	57M	LCx: 100% mid 1/3	98	5	101	0.54	117	0.15
21	34M	RCA: 100% prox 1/3	75	4	68	0.48	99	0.10
22	43M	RCA: >50-<90% mid 1/3	82	6	90	0.37	95	0.08
23	63F	RCA: >50-<90% mid 1/3	56	12	103	0.47	113	...
Mean ± SD	47 ± 9		82 ± 20	10 ± 4	93 ± 26	0.40 ± 0.11	110 ± 21	0.11 ± 0.09

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; mid = middle; prox = proximal; RCA = right coronary artery. Other abbreviations as in Table I.

One vessel disease: The data for 23 patients with one vessel disease are presented in Table II. In 16 patients the lesions were in the proximal third of the vessel. Seven of 11 patients without a myocardial infarction had lesions occluding 90 percent or more of the coronary arterial lumen, and 7 of 12 patients with infarction had either 90 percent or greater stenosis or total occlusion.

Two vessel disease: Table III presents data for the group of 25 patients with two vessel disease. Five of the 13 patients without evidence of prior myocardial infarction had a 90 percent or greater lesion in both involved vessels, and 5 patients a 90 percent or greater lesion in one of the two vessels. The lesions were located in the proximal third in 20 of the 26 diseased vessels in this subgroup. Two of the 12 patients with infarction had 100 percent occlusion of both vessels, and 8 had 100 percent occlusion of one vessel. The lesions were in the proximal third in 14 of the 24 diseased arteries.

Three vessel disease: Table IV summarizes the arteriographic and hemodynamic data in the 34 patients with three vessel disease. In 39 of the 51 involved vessels in patients without infarction the lesions were proximal; 12 vessels were totally occluded and 6 had 90 percent or greater stenosis. Four patients had a significant lesion of the left main coronary artery. Among patients with infarction, the lesion was proximal in 39 of the 52 vessels studied; 22 vessels were totally occluded. Every patient had total occlusion of at least one vessel, and seven had total occlusion of two of the three vessels. Patient 25 (Table IVB) had also been studied before myocardial infarction occurred (Patient 14, Table IVA).

Comparison of normal subjects and patients with coronary disease: Table V compares each group of patients with the 15 normal subjects. Age and heart rate during left ventricular angiography were comparable for each group and for patients with and without infarction within each vessel disease group. Left ventricular end-diastolic pressure was elevated by comparison with values in normal subjects in the group with three vessel disease and infarction (17 ± 8 [standard deviation] mm Hg, $P < 0.0001$). Left ventricular end-diastolic volume was increased in patients with infarction in all vessel disease groups: 93 ± 26 ml/m^2 ($P < 0.01$), 95 ± 25 ml/m^2 ($P < 0.01$) and 99 ± 24 ml/m^2 ($P < 0.0005$) in those with one, two and three vessel disease, respectively. The ejection fraction was significantly depressed in all patients with three vessel disease and in those with infarction and one or two vessel disease. Left ventricular mass was increased in all patients with three vessel disease: 114 ± 36 and 113 ± 30 g/m^2 ($P < 0.05$), respectively, in patients without and with infarction. Left ventricular compliance was significantly reduced only in patients with infarction: 0.11 ± 0.09 ($P < 0.01$); 0.12 ± 0.10 ($P < 0.05$); and 0.06 ± 0.05 ($P < 0.0001$), respectively, in patients with one, two or three vessel disease. The significant differences observed between the data of patients with and without infarction within each vessel disease group are also shown. Left ventricular end-diastolic pressure increased in the presence of myocardial infarction only in patients with three vessel disease ($P < 0.0001$). Left ventricular end-diastolic volume was greater in patients with myocardial infarction than in those without infarction in each of the vessel disease groups ($P < 0.005$ for one and two vessel disease and $P < 0.001$ for three vessel disease). Ejection fraction was lower in patients with infarction within the three groups. Even in patients with three vessel disease the reduced ejection fraction decreased further with myocardial infarction. Left ventricular mass increased within the one vessel disease group when infarction was present. In all patients with three vessel disease left ventricular mass was increased and did not increase further with myocardial infarction. Left ventricular compliance was decreased in the groups with myocardial infarction in patients with two ($P < 0.05$) and three ($P < 0.0005$) vessel disease.

Discussion

Natural History

Role of severity and extent of coronary disease: Coronary artery disease produces such a spectrum of left ventricular dysfunction with or without myocardial infarction that it is difficult to determine disability and establish a prognosis for an individual patient. Friesinger et al.[1] have shown that mortality is related to the severity of coronary arterial obstruction; their patients with one vessel disease had a low incidence of myocardial infarction and did not die of coronary artery disease during the 54 month observation period. Oberman et al.[2] reported respective mortality rates of 4, 26 and 29 percent in patients with one, two and three vessel disease, during a follow-up period of approximately 22 months. Bruschke et al.[3] reported respective mortality rates of 4 and 15 percent 2 and 5 years after arteriography in patients with one vessel disease. With moderate narrowing (greater than 30 to less than 50 percent) of other vessels the 5 year mortality rate increased from 15 to 23 percent. Among patients with two vessel disease the mortality rate at 2 years was 21 percent and at 5 years 38 percent; among those with three vessel disease the respective mortality rates were 33 and 54 percent. In Bruschke's series,[3] patients with a history of a single myocardial infarction had a 5 year mortality rate of 43 percent; in those with a history of more than one infarct, the rate was 49 percent. In contrast, patients without prior myocardial infarction had a 5 year mortality rate of 29 percent. These mortality figures were not related to the number of diseased vessels. Oberman et al.[2] reported that in patients with one vessel disease and electrocardiographic evidence of myocardial infarction the mortality rate at 2 years was 13 percent compared with 100 percent survival of patients without electrocardiographic evidence of in-

TABLE III

Data in 25 Patients With Two Vessel Disease

Case no.	Age (yr) & Sex	Coronary Stenosis	HR	LVEDP	LVEDV	EF	LV Mass	LV Compliance
		A. 13 Patients Without Myocardial Infarction						
1	51M	LAD: 100% prox 1/3 LCx: 100% prox 1/3	90	15	82	...	92	...
2	57M	LAD: >50–<90% prox 1/3 LCx: ≥90% prox 1/3	59	26	66	0.52	92	0.09
3	41M	LAD: >50–<90% prox 1/3 LCx: ≥ 90% prox 1/3	67	11	89	0.56	98	0.18
4	49M	LAD: >50–<90% prox 1/3 LCx: >50–<90% prox 1/3	72	10	67	0.47	116	...
5	48F	LAD: >50–<90% prox 1/3 LCx: >50–<90% prox 1/3	75	10	56	0.56	112	0.34
6	52M	LAD: ≥90% prox 1/3 LCx: 50% mid 1/3	71	9	62	0.53	102	0.11
7	43M	LAD: ≥90% prox 1/3 RCA: 100% mid 1/3	63	15	80	0.48	102	0.10
8	63F	LAD: >50–<90% prox 1/3 RCA: 50% prox 1/3	88	3	60	0.52	64	0.28
9	52M	LAD: ≥90% prox 1/3 RCA: ≥90% mid 1/3	90	8	69	0.50	103	0.24
10	42M	LAD: ≥90% prox 1/3 RCA: ≥90% mid 1/3	86	7	87	0.67	108	0.27
11	61M	LAD: ≥90% prox 1/3 RCA: >50–<90% prox 1/3	63	8	61	0.56	69	...
12	59M	LCx: ≥90% prox 1/3 RCA: 100% mid 1/3	75	13	74	0.66	104	0.12
13	37M	LCx: 100% mid 1/3 RCA: >50–<90% prox 1/3	95	7	86	...	92	...
Mean ± SD	50 ± 8		76 ± 12	11 ± 6	72 ± 11	0.55 ± 0.07	96 ± 15	0.19 ± 0.09
		B. 12 Patients With Myocardial Infarction						
14	61M	LAD: 100% prox 1/3 LCx: 100% prox 1/3	86	20	82	0.38	114	0.03
15	46M	LAD: 100% prox 1/3 LCx: 100% dist 1/3	91	25	136	0.23	105	0.02
16	50M	LAD: ≥90% mid 1/3 LCx: 100% mid 1/3	71	2	65	0.59	75	0.28
17	42F	LAD: >50–<90% mid 1/3 LCx: 100% mid 1/3	107	1	64	0.52	69	0.24
18	47M	LAD: 100% prox 1/3 RCA: 50% mid 1/3	71	15	70	0.44	68	0.26
19	61M	LAD: >50–<90% mid 1/3 RCA: 100% prox 1/3	68	11	124	0.36	171	0.03
20	44M	LAD: >50–<90% mid 1/3 RCA: 50% mid 1/3	78	10	90	0.42	152	0.13
21	34M	LCx: 100% prox 1/3 RCA: >50–<90% prox 1/3	57	14	126	0.47	105	0.07
22	38M	LCx: ≥90% prox 1/3 RCA: 100% prox 1/3	92	6	120	0.32	130	0.05
23	34M	LCx: ≥90% prox 1/3 RCA: 100% prox 1/3	93	6	91	0.19	104	0.07
24	47M	LCx: >50–<90% prox 1/3 RCA: 100% mid 1/3	80	9	82	0.33	87	...
25	41M	LCx: 50% prox 1/3 RCA: ≥90% prox 1/3	80	3	86	0.44	80	0.13
Mean ± SD	45 ± 9		81 ± 14	10 ± 7	.95 ± 25	0.39 ± 0.11	105 ± 33	0.12 ± 0.10

dist = distal. Other abbreviations as in Tables I and II.

TABLE IV

Data in 34 Patients With Three Vessel Disease

Case no.	Age (yr) & Sex	Coronary Stenosis	HR	LVEDP	LVEDV	LV EF	LV Mass	LV Compliance
		A. 17 Patients Without Myocardial Infarction						
1	53F	LCA: ≥90% LAD: >50–<90% prox 1/3 RCA: 100% prox 1/3	90	1	38	0.50	...	0.34
2	54M	LCA: ≥ 90% LAD: >50–<90% prox 1/3 RCA: 50% prox 1/3	61	8	81	0.52	112	0.21
3	53M	LCA: ≥90% RCA: >50–<90% prox 1/3	91	9	61	0.38	63	0.14
4	42M	LCA: >50–<90% LAD: 50% prox 1/3 LCx: >50–<90% dist 1/3 RCA: 100% prox 1/3	63	15	89	0.48	105	0.10
5	59M	LAD: 100% prox 1/3 LCx: >50–<90% prox 1/3 RCA: ≥90% prox 1/3	61	9	73	0.42	100	...
6	51M	LAD: ≥90% prox 1/3 LCx: >50–<90% prox 1/3 RCA: 100% prox 1/3	95	10	81	0.46	88	0.24
7	53M	LAD: 100% prox 1/3 LCx: >50–<90% prox 1/3 RCA: >50–<90% prox 1/3	75	9	88	0.42	94	0.12
8	47M	LAD: >50–<90% prox 1/3 LCx: ≥90% prox 1/3 RCA: 100% prox 1/3	87	9	76	0.40	147	0.16
9	65F	LAD: 50% prox 1/3 LCx: 100% prox 1/3 RCA: ≥90% prox 1/3	67	10	118	0.31	205	0.10
10	57M	LAD: ≥90% prox 1/3 LCx: >50–<90% prox 1/3 RCA: >50–<90% prox 1/3	88	8	81	0.56	...	0.22
11	65M	LAD: >50–<90% prox 1/3 LCx: >50–<90% prox 1/3 RCA: >50–<90% prox 1/3	86	4	80	0.35	114	0.14
12	49M	LAD: 100% prox 1/3 LCx: >50–<90% dist 1/3 RCA: >50–<90% prox 1/3	82	13	78	0.58	...	0.16
13	45M	LAD: >50–<90% prox 1/3 LCx: 100% prox 1/3 RCA: >50–<90% prox 1/3	58	7	73	0.57	91	0.17
14*	43M	LAD: 100% prox 1/3 LCx: >50–<90% mid 1/3 RCA: >50–<90% dist 1/3	86	10	73	0.37	82	0.09
15	46M	LAD: 100% prox 1/3 LCx: >50–<90% mid 1/3 RCA: >50–<90% prox 1/3	118	3	69	0.46	155	0.17
16	61M	LAD: ≥90% prox 1/3 LCx: >50–<90% dist 1/3 RCA: >50–<90% prox 1/3	72	4	64	0.43	113	0.13
17	47M	LAD: 100% mid 1/3 LCx: ≥90% mid 1/3 RCA: 100% prox 1/3	59	6	89	0.50	121	0.16
Mean ± SD	52 ± 7		79 ± 16	8 ± 4	77 ± 16	0.45 ± 0.08	114 ± 36	0.17 ± 0.06
		B. 17 Patients With Myocardial Infarction						
18	53M	LCA: 50% LAD: 100% prox 1/3 LCx: 100% prox 1/3 RCA: >50–<90% prox 1/3	65	15	125	0.34	134	0.02

Case no.	Age (yr) & Sex	Coronary Stenosis	HR	LVEDP	LVEDV	LV EF	LV Mass	LV Compliance
19	46F	LAD: 100% prox 1/3 LCx: >50-<90% prox 1/3 RCA: 100% prox 1/3	97	28	131	0.14	145	0.01
20	53M	LAD: 100% prox 1/3 LCx: 50% prox 1/3 RCA: 100% prox 1/3	62	22	117	0.28	171	0.04
21	51M	LAD: >50-<90% prox 1/3 LCx: 100% prox 1/3 RCA: >50-<90% prox 1/3	79	25	97	0.35	108	0.03
22	49M	LAD: >50-<90% prox 1/3 LCx: >50-<90% prox 1/3 RCA: 100% prox 1/3	89	10	82	0.47	94	0.06
23	35M	LAD: 50% prox 1/3 LCx: >50-<90% prox 1/3 RCA: 100% prox 1/3	95	11	83	0.38	104	0.14
24	38M	LAD: 100% prox 1/3 LCx: 100% prox 1/3 RCA: >50-<90% mid 1/3	83	12	71	0.42	107	0.08
25*	44M	LAD: 100% prox 1/3 LCx: 100% prox 1/3 RCA: >50-<90% mid 1/3	65	22	119	0.26	94	0.02
26	36M	LAD: 100% prox 1/3 LCx: 50% mid 1/3 RCA: 100% prox 1/3	75	14	66	0.45	95	0.05
27	67F	LAD: >50-<90% prox 1/3 LCx: >50-<90% mid 1/3 RCA: 100% prox 1/3	68	8	79	0.46	112	0.11
28	44M	LAD: >50-<90% mid 1/3 LCx: >50-<90% prox 1/3 RCA: 100% prox 1/3	94	29	88	0.33	...	...
29	54M	LAD: >50-<90% prox 1/3 LCx: >50-<90% mid 1/3 RCA: 100% prox 1/3	73	4	97	0.36	113	0.15
30	64M	LAD: >50-<90% mid 1/3 LCx: 100% prox 1/3 RCA: 50% mid 1/3	59	19	99	0.44	60	...
31	51M	LAD: >50-<90% prox 1/3 LCx: >50-<90% prox 1/3 RCA: 100% mid 1/3	72	30	129	0.27	122	0.03
32	41M	LAD: ≥90% prox 1/3 LCx: 100% mid 1/3 RCA: 100% prox 1/3	89	25	149	0.23	170	0.02
33	55M	LAD: ≥90% prox 1/3 LCx: ≥90% mid 1/3 RCA: 100% prox 1/3	75	8	77	0.35	88	0.10
34	34M	LAD: >50-<90% mid 1/3 LCx: ≥90% prox 1/3 RCA: 100% prox 1/3	75	11	81	0.41	96	...
Mean ± SD	48 ± 10		77 ± 12	17 ± 8	99 ± 24	0.35 ± 0.09	113 ± 30	0.06 ± 0.05

* Same patient studied before (Case 14) and after (Case 25) myocardial infarction.
LCA = left main coronary artery. Other abbreviations as in Tables I to III.

farction. In patients with two and three vessel disease the mortality increased two-fold with electrocardiographic evidence of infarction.

Role of left ventricular dysfunction: The importance of left ventricular dysfunction is revealed in Oberman's series.[2] Forty percent of patients with dyspnea on exertion and paroxysmal nocturnal dyspnea or orthopnea died within 2 years of arteriographic diagnosis of coronary artery disease; the 2 year mortality rate in patients without these symptoms was 8 percent. The presence of cardiomegaly increased the mortality rate from 3 to 23 percent.

TABLE V

Summary of Hemodynamic Data

	Normal (15)	One Vessel Disease		Two Vessel Disease		Three Vessel Disease	
		No MI (11)	MI (12)	No MI (13)	MI (12)	No MI (17)	MI (17)
Age (yr)							
Mean ± SD	45 ± 8	50 ± 6	47 ± 9	50 ± 8	45 ± 9	52 ± 7	48 ± 10
Range	33–59	42–62	34–63	37–63	34–61	42–65	34–67
P_1	...	NS	NS	NS	NS	NS	NS
P_2	...	...	NS	...	NS	...	NS
Heart rate							
Mean ± SD	78 ± 16	82 ± 11	82 ± 20	76 ± 12	81 ± 14	79 ± 16	77 ± 12
Range	52–111	67–106	56–112	59–95	57–107	58–118	59–97
P_1	...	NS	NS	NS	NS	NS	NS
P_2	...	...	NS	...	NS	...	NS
LVEDP (mm Hg)							
Mean ± SD	7 ± 4	8 ± 6	10 ± 4	11 ± 6	10 ± 7	8 ± 4	17 ± 8
Range	2–12	4–23	4–16	3–26	1–25	1–15	4–30
P_1	...	NS	NS	NS	NS	NS	<0.0001
P_2	...	...	NS	...	NS	...	<0.0001
LVEDV (ml/m²)							
Mean ± SD	71 ± 13	67 ± 12	93 ± 26	72 ± 11	95 ± 25	77 ± 16	99 ± 24
Range	39–90	49–95	62–155	56–89	64–136	38–118	66–149
P_1	...	NS	<0.01	NS	<0.01	NS	<0.0005
P_2	...	...	<0.005	...	<0.005	...	<0.001
LV EF							
Mean ± SD	0.55 ± 0.04	0.54 ± 0.05	0.40 ± 0.11	0.54 ± 0.06	0.39 ± 0.11	0.45 ± 0.08	0.35 ± 0.09
Range	0.50–0.64	0.47–0.64	0.14–0.54	0.47–0.67	0.19–0.59	0.31–0.58	0.14–0.47
P_1	...	NS	<0.0001	NS	<0.0001	<0.001	<0.0001
P_2	...	...	<0.0005	...	<0.0001	...	<0.001
LV mass (g/m²)							
Mean ± SD	92 ± 21	87 ± 14	110 ± 21	96 ± 15	105 ± 33	114 ± 36	113 ± 30
Range	48–130	67–110	83–163	64–116	68–171	63–205	60–171
P_1	...	NS	NS	NS	NS	<0.05	<0.05
P_2	...	...	<0.05	...	NS	...	NS
LV compliance							
Mean ± SD	0.20 ± 0.09	0.19 ± 0.06	0.11 ± 0.09	0.19 ± 0.09	0.12 ± 0.10	0.17 ± 0.06	0.06 ± 0.05
Range	0.11–0.39	0.12–0.33	0.02–0.29	0.09–0.34	0.02–0.28	0.09–0.34	0.01–0.15
P_1	...	NS	<0.01	NS	<0.05	NS	<0.0001
P_2	...	...	NS	...	<0.05	...	<0.0005

Figures in parentheses indicate number of patients.

MI = myocardial infarction; NS = not significant; P_1 = P value, comparison with normal group; P_2 = P value, comparison within each vessel disease group.

TABLE VI

Effect of Severity of Coronary Disease and Myocardial Infarction on Left Ventricular Function

Parameter	Change	Disease Group
LVEDP	↑	3 vessel disease with MI
LVEDV	↑	1, 2, 3 vessel disease with MI
LV mass	↑	3 vessel disease with and without MI
LVEF	↓	1, 2, 3 vessel disease with MI
	↓	3 vessel disease without MI
LV compliance	↓	1, 2, 3 vessel disease with MI

↑ = abnormally elevated or increased; ↓ = abnormally decreased.

MI = myocardial infarction.

Bruschke et al.[4] reported that 17 of 32 patients with clinical congestive heart failure died in the first year after cardiac catheterization and that 84 percent were dead at 5 years. It is of note that five of these patients had only one vessel disease.

Qualitative analysis of single plane left ventricular angiograms in 527 of the 590 patients of Bruschke et al. demonstrated increasing mortality as abnormality in ventricular contraction increased. In 54 patients with a diffuse contraction abnormality the 5 year mortality rate was 71 percent although 30 of these patients apparently did not have clinical evidence of left ventricular failure. There is strong evidence that surgical mortality is more highly related to left ventricular function than to the extent of coronary artery disease or the patency of vein grafts.[5–8] Seven of nine patients reported by Kouchoukos et al.[7] to have

an ejection fraction of less than 0.22 died within 4 months of operation: All vein grafts were patent at postmortem examination. In a large series studied by Spencer et al.[8] the mortality rate 1 year after operation was 57 percent in patients with severe heart failure. Thus, the relation between left ventricular function and the presence or absence of previous myocardial infarction in patients with coronary artery disease is clinically important.

Role of Myocardial Infarction

Left ventricular end-diastolic pressure: In our study left ventricular end-diastolic pressure was increased only in patients with three vessel disease and myocardial infarction. Patients with one or two vessel disease and infarction with significantly increased left ventricular end-diastolic volume and reduced ejection fraction did not have significantly increased left ventricular end-diastolic pressure.

Left ventricular end-diastolic pressure has serious limitations as an index of myocardial function in patients with chronic heart disease. Rackley et al.[19] found no relation between left ventricular end-diastolic pressure and left ventricular end-diastolic volume, left ventricular mass or ejection fraction in patients with mitral stenosis, idiopathic myocardial hypertrophy, primary myocardial disease, compensated and decompensated volume overload and pressure overload. Braunwald and Ross[20] emphasized that hypervolemic states and pericardial constriction could be associated with increased left ventricular end-diastolic pressure without impairment of cardiac performance. Hamby et al.[21] reported that left ventricular end-diastolic pressure is increased in patients with disease limited to the left anterior descending coronary artery as well as in patients with lesions in more than one vessel, but their study did not separate patients with and without myocardial infarction. Hamilton et al.[22] found increased left ventricular end-diastolic pressure in patients with probable or definite infarction, but their study did not take into account the number of diseased vessels. Feild et al.[23] quantitated the size of the myocardial scar and observed that an akinetic or dyskinetic segment greater than 15 percent of the end-diastolic circumference of the left ventricle was associated with a left ventricular end-diastolic pressure greater than 12 mm Hg.

Left ventricular end-diastolic volume: This variable was elevated in our patients with one, two and three vessel disease who had had a myocardial infarction. Hamilton et al.[22] also found that patients with infarction have increased left ventricular volume. This increase may reflect compensation by the ventricle with localized contraction abnormalities in order to maintain a normal stroke volume and left ventricular end-diastolic pressure. Feild et al.[23] demonstrated that patients with abnormally contracting segments involving more than 17 percent of the end-diastolic circumference of the left ventricle had increased left ventricular end-diastolic volume. However, in the review of Baxley et al.[24]; 12 patients had increased left ventricular volume in the absence of localized contraction abnormalities. In our series ventricular dilatation did not prevent an increase in left ventricular end-diastolic pressure in patients with three vessel disease and myocardial infarction (Table V), although in patients with one and two vessel disease and myocardial infarction, an increase in ventricular end-diastolic volume may be maintaining a normal end-diastolic pressure.

Ejection fraction: In our series left ventricular ejection fraction was reduced in all patients who had sustained a myocardial infarction as well as in patients with three vessel disease who had no history of infarction (Table V). There was also a significant depression of ejection fraction within each of the groups when infarction occurred. The depressed ejection fraction in patients with three vessel disease and no myocardial infarction further decreased in the presence of infarction. This finding is in agreement with the data of Baxley et al.,[24] who found a depressed ejection fraction in patients with definite or probable myocardial infarction by comparison with patients without infarction. Our findings suggest that the ejection fraction is more sensitive than dilatation or increased left ventricular end-diastolic pressure in measuring abnormalities in left ventricular function after myocardial infarction.

Left ventricular mass: Myocardial hypertrophy may occur with total occlusion of coronary arteries in the presence of myocardial scarring due to infarction.[25] In our series of patients there was a significant increase in left ventricular mass in patients with three vessel disease with or without myocardial infarction. Similarly, Rackley et al.[26] found an increase in left ventricular mass in 17 of 23 patients with severe coronary artery disease. Among our patients with one vessel disease, left ventricular mass was greater in those with myocardial infarction. This finding seems to indicate that the mechanism of compensatory hypertrophy is retained in patients with disease of only one vessel.

Left ventricular compliance: This variable was significantly lower than normal in our patients with one, two and three vessel disease after the occurrence of myocardial infarction (Table V). Among patients with two and three vessel disease, left ventricular compliance was lower in patients with myocardial infarction than in those without infarction. This loss of ventricular distensibility resulting in reduced left ventricular compliance may be due to several factors.[17] Reduced compliance correlates inversely with abnormally contracting segments of myocardium, that is, hypokinetic, akinetic or dyskinetic areas. Smith et al.[17] found that left ventricular compliance was reduced when the abnormally contracting segment exceeded 8 percent of the end-diastolic circumference of the left ventricle. Normal compliance in patients with coronary disease but without infarction would seem to eliminate the speculation that small zones of myocardial disease can decrease left ventricular distensibility.

Clinical implication: Evaluation of patients with coronary artery disease should include an effort to document previous myocardial infarction during the patient's clinical course. Our data indicate that myocardial infarction can decrease left ventricular function, as expressed by decreases in ejection fraction and left ventricular compliance, even in patients with one and two vessel coronary artery disease (Table VI).

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Improvement of Reduced Left Ventricular Diastolic Compliance in Ischemic Heart Disease After Successful Coronary Artery Bypass Surgery

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To determine the effects of myocardial revascularization on decreased left ventricular diastolic compliance consequent to chronic stable coronary artery disease, 15 patients with patent coronary artery bypass grafts (Group I) were compared with 8 patients with occluded grafts (Group II) studied before and after operation. In addition, eight normal patients served as controls. Left ventricular diastolic compliance was assessed by: (1) total observed diastolic compliance: stroke volume (V) related to left ventricular diastolic pressure (P) change ($\Delta V/\Delta P$) normalized for end-systolic volume; (2) left ventricular stiffness index of passive elastic modulus (a = slope of $\Delta P/\Delta V$ related to mean left ventricular diastolic pressure); and (3) fractional pattern of left ventricular filling. All patients had normal sinus rhythm and none had preoperative or postoperative mitral regurgitation. The two groups with coronary disease were well matched preoperatively for ventricular function, volumes, mass, segmental contraction and compliance. Ejection fraction increased in Group I (0.56 preoperatively to 0.65 postoperatively, $P < 0.05$) but was unchanged in Group II (0.63 to 0.61, $P > 0.05$). Postoperative indexes of left ventricular compliance improved in Group I: (1) 0.110 to 0.150 ($P < 0.05$); (2) 0.030 to 0.019 ($P < 0.05$); and (3) 37 to 30 percent filling during last one third of diastole ($P < 0.05$). These indexes were unchanged postoperatively in Group II: (1) 0.109 to 0.102 ($P > 0.05$); (2) 0.033 to 0.039 ($P > 0.05$); and (3) 36 to 41 percent ($P > 0.05$). Compliance indexes were not altered ($P > 0.05$) in a subset of seven patients in Group I with preoperative or intercurrent myocardial infarction. Thus, this investigation demonstrates the relatively reversible nature of abnormal left ventricular compliance after successful coronary artery bypass surgery in certain patients with ischemic heart disease.

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The effects of myocardial revascularization on altered left ventricular diastolic compliance in coronary artery disease are unknown. Although previous clinical observations have documented improvement in hemodynamic data and other variables of contraction after restoration of myocardial perfusion in coronary disease,[1-3] information pertaining to possible reversibility of abnormal left ventricular distensibility is lacking. Further, amelioration of pulmonary congestion after coronary artery bypass surgery may be related to improved compliance of the ventricle, with consequent favorable alterations of its passive pressure-volume relation, in addition to enhancement of cardiac contractile properties. This investigation was carried out to determine whether, and to what degree, abnormalities of diastolic compliance in patients with chronic ischemic heart disease are in-

fluenced by successful coronary artery bypass surgery.

Material and Methods

Case material: Twenty-three patients with chronic stable coronary artery disease who underwent left heart catheterization and selective coronary arteriography preoperatively and an average of 17 weeks after coronary artery bypass surgery comprised the study group. To evaluate the effects of revascularization on left ventricular compliance, patients with patency of all bypass grafts (Group I) were compared with patients with occlusion of all bypass grafts (Group II). As indicated in detail later, the groups were well matched preoperatively for ventricular function, volumes, mass, segmental contraction, diastolic compliance and stiffness. Restudy was carried out 2 to 114 weeks (mean 19 weeks) postoperatively in Group I and 2 to 70 weeks (mean 15 weeks) postoperatively in Group II.

Group I consisted of 15 consecutive patients with patent saphenous vein grafts or left internal mammary artery anastomoses to the left anterior descending coronary artery; six had one or two additional patent vein grafts to the left circumflex or right coronary arterial systems, or both. Group II was composed of eight consecutive patients with obstruction of all grafts or anastomoses including, in each, a bypass graft to the left anterior descending coronary artery. All 23 patients had normal sinus rhythm and none had mitral regurgitation as assessed by left ventricular angiography before and after operation. Before operation, the average number of the three major coronary arteries with significant (75 percent or greater) proximal stenosis was 2.2 in patients with patent bypass grafts (Group I) and 2.6 in patients with nonpatent grafts (Group II) ($P > 0.05$). The mean number of saphenous vein grafts or internal mammary artery to left anterior descending coronary artery anastomoses, or both, was 1.6 in the patients with patent grafts and 1.7 in those with occluded grafts ($P > 0.05$). Four patients in Group I and three in Group II had preoperative electrocardiographic evidence of myocardial infarction with corresponding regional contraction abnormalities by left ventriculography. Three additional patients in Group I and two others in Group II had electrocardiographic evidence of intraoperative or postoperative myocardial infarction. Eight patients with normal findings on selective coronary arteriography and normal left ventricular function served as controls.

Methods of determining ventricular function and compliance: Biplane left ventricular cineangiography was performed before and after operation in the 30° right anterior oblique and 60° left anterior oblique projections utilizing 1.0 cc/kg of Hypaque-M® 75 percent (Winthrop) containing sodium and meglumine diatrizoates injected at 300 lb/in^2 through an angiographic catheter. Left ventricular volumes and mass were determined using the single plane, right anterior oblique method.[4–6] Left ventricular pressure was obtained by use of a high fidelity micromanometer catheter (Statham SF1) or fluid-filled catheter system, or both, with directly attached external low volume displacement transducer (Microdot MS-5).[7] In the patients whose left ventricular diastolic pressure was recorded by both the intracardiac and external manometers, there were no significant differences between the indexes of compliance calculated by the two systems at a single catheterization.

Three different physiologic expressions of compliance were utilized to evaluate the passive pressure-volume characteristics of the left ventricle. In the first method,[8,9] total observed diastolic compliance (distensibility) was obtained as $\Delta V/\Delta P$, where ΔV equals diastolic volume change measured as stroke index, determined from cardiac output measured by left ventricular-injected dye-dilution technique corrected for body surface area; and ΔP equals change in left ventricular diastolic pressure, measured from the lowest early diastolic pressure to end-diastole 0.04 second after onset of the QRS complex. Three consecutive left ventricular beats immediately before and after the cardiac output determinations were averaged for $\Delta V/\Delta P$ for each patient. Since initial ventricular volume influences the functional passive pressure-volume curve, the value for observed compliance was normalized by end-systolic volume index (ESVI): $\Delta V/(\Delta P \times ESVI)$.[8,9]

In the second method, the reciprocal of compliance, diastolic stiffness ($\Delta P/\Delta V$), was evaluated by determination of the left ventricular passive elastic modulus *(a)*. Previous studies in the canine heart have shown that the instantaneous first derivative of the diastolic pressure-volume curve (dP/dV) related to simultaneous ventricular pressure (P) is a linear function, the slope (a constant) of which provides a quantitative index of left ventricular wall stiffness, independent of ventricular volume and largely independent of chamber geometry.[10,11] This approach has been extended to the relation of $\Delta P/\Delta V$ to mean left ventricular diastolic pressure ($\bar{P}$),[12] where ΔP is total change in diastolic pressure and ΔV stroke index, determined as before for observed compliance. As with (dP/dV)/P in single beats,[10,11] $(\Delta P/\Delta V)/\bar{P}$ obtained from a group of ventricles delineates a characteristic linear relation, and its slope (the passive elastic modulus) is specific among normal hearts and is distinctive for ventricles with a given disease process depending on relative chamber stiffness.[12] The passive elastic modulus has been demonstrated to be more sensitive than the diastolic pressure-volume curve to alterations in ventricular stiffness,[10,11] and use of this slope constant obviates the difficulties inherent in quantification and interpretation of the curvilinear passive pressure-volume relation.

An additional means of assessing ventricular stiffness and distensibility is determination of the temporal pattern of filling of the chamber in terms of volume increments during sequential intervals of diastole.[13,14] This method has been applied previously in comparison of patients with mitral insufficiency, aortic stenosis and coronary artery disease,[13] as well as those with various degrees of severity of ischemic heart disease.[14] With use of the right anterior oblique single plane technique,[4,6] fractional increments of left ventricular volume were measured at the end of early, middle and late diastole and the percent of diastolic filling was determined for each of these three equal time periods (method three).

Results

Ventricular Function

In the 15 patients with patent grafts by arteriography (Group I), ejection fraction increased from the preoperative value of 0.56 to 0.65 after operation ($P < 0.01$) (Fig. 1). In contrast, there was no significant change in this variable at postoperative catheterization in the eight patients with graft occlusion (Group II) (0.63 to 0.61, $P > 0.05$).

In Group I, there were no significant changes ($P > 0.05$) from pre- to postoperative values for left ventricular end-diastolic volume index (89 to 86 cc/m^2), left ventricular mass (116 to 112 g/m^2), left ventricular wall thickness (15.1 to 14.7 mm), heart rate (87 to 84 beats/min) or diastolic filling rate (stroke index/

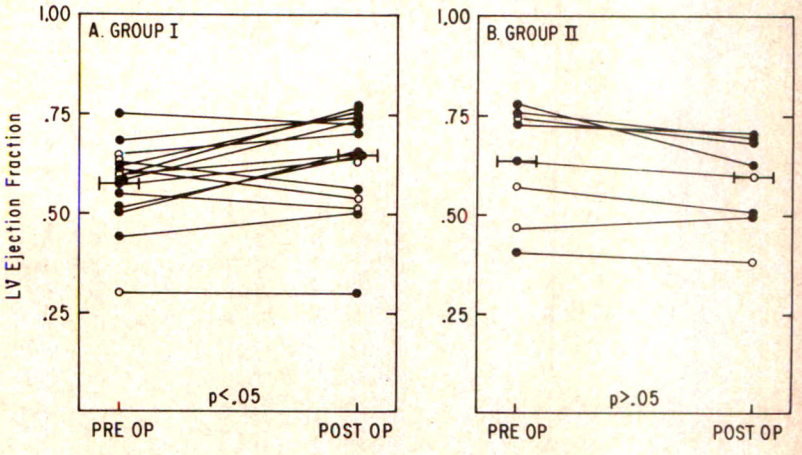

FIGURE 1. Effects of coronary artery bypass surgery on left ventricular (LV) ejection fraction in patients with patent (Group I, panel **A**) bypass grafts and occluded (Group II, panel **B**) bypass grafts. Post op = postoperative; pre op = preoperative. **Open circles** denote patients with pre- or postoperative myocardial infarction.

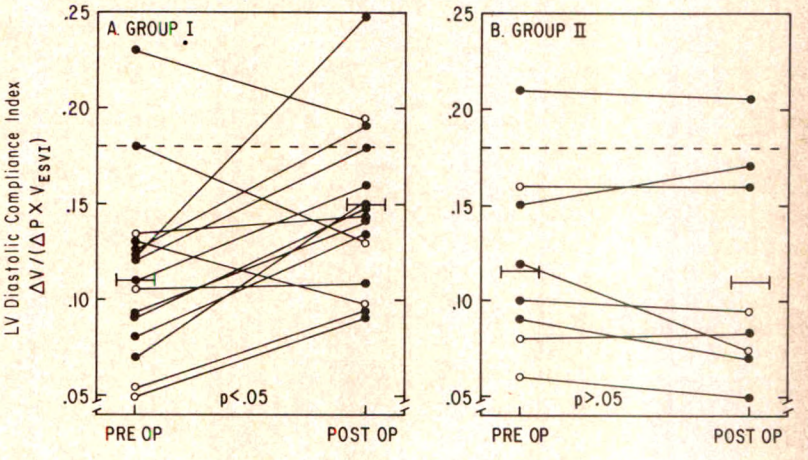

FIGURE 2. Effects of coronary artery bypass surgery on total observed left ventricular diastolic compliance in patients with patent (Group I, panel **A**) and occluded (Group II, panel **B**) bypass grafts. The **horizontal broken lines** indicate the mean value for eight normal patients; **open circles** indicate patients with pre- or postoperative myocardial infarction.

diastolic filling period) (91.3 to 95.6 cc/m^2 per sec). Further, the differences between these variables in the two groups were not statistically significant (P >0.05) before or after operation.

Total Observed Diastolic Compliance

The eight normal patients had a total left ventricular diastolic compliance index of 0.180. In contrast, the patients in Groups I and II had respective preoperative values of 0.110 and 0.121 (P <0.01 compared with values in normal subjects) (Fig. 2). There was no significant difference (P >0.05) between the low compliance values in Groups I and II. After operation, the compliance index increased to 0.150 (P <0.05) in the patients with open grafts; those with bypass occlusion had no significant change (0.112, P >0.05) (Fig. 2). The postoperative compliance index was significantly lower (P <0.05) than normal in Group I.

In Group I, the compliance index was lower in the 4 patients who had preoperative myocardial infarction than in the 11 patients without preoperative infarction (0.085 vs. 0.123, P <0.05) (Fig. 2). In the subset of seven patients in Group I with preoperative or intercurrent myocardial infarction, compliance was increased postoperatively in only three patients, and the values for the subset were not altered significantly (0.087 to 0.099, P >0.05) (Fig. 2). In contrast, there was a marked increase in compliance in the eight patients without myocardial necrosis (0.109 to 0.179, P <0.01).

Passive Elastic Modulus

There was a general linear relation between $\Delta P/\Delta V$ and $\bar{P}$ in each group (Fig. 3). Preoperatively, the stiffness index of passive elastic modulus (a slope constant of the $\Delta P/\Delta V$ to $\bar{P}$ ratio) in Group I (0.030; Fig. 3A) was the same as that in Group II (0.033, P >0.05; Fig. 3C). After successful bypass surgery in patients in Group I, the passive elastic modulus slope decreased to 0.019 (P <0.05; Fig. 3B), but this variable was unchanged postoperatively in patients in Group II (0.032, P >0.05) (Fig. 3D). The passive elastic modulus value of 0.009 in the normal patients was significantly lower (P <0.01) than that of patients in either of the two groups with coronary disease preoperatively or Group II postoperatively, and it was also lower (P <0.05) than that of patients in Group I after operation. It was higher in Group I patients with preoperative myocardial infarction than in those without infarction (0.041 and 0.026, P <0.05) (Fig. 3A) and postoperatively was higher in patients with pre- or postoperative infarction than in those without infarction (0.034 and 0.009, P <0.05) (Fig. 3B).

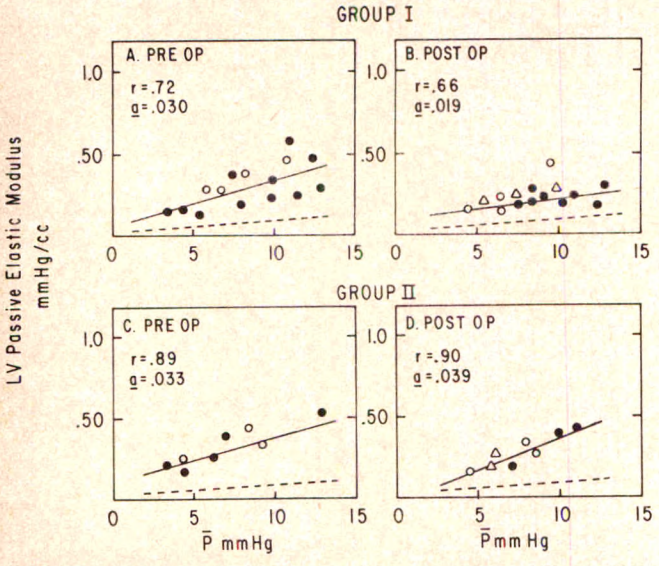

FIGURE 3. Effects of coronary artery bypass surgery on the relation between left ventricular diastolic stiffness ($\Delta P/\Delta V$) and mean left ventricular diastolic pressure ($\bar{P}$) in patients with patent grafts (Group I) and in those with occluded grafts (Group II). The slope of this linear regression (a = passive elastic modulus) is a specific index of wall stiffness. The passive elastic modulus for eight normal patients (a = 0.009) is indicated by the **dashed lines. Open circles** denote preoperative myocardial infarction; **open triangles** indicate postoperative infarction.

Ventricular Filling Pattern

Characterization of the pattern of ventricular filling by fractional increments of volumes for three successive equal-time segments of diastole in the normal patients showed greater filling in the early and middle periods of diastole relative to the final third: 34, 38 and 28 percent, respectively (P <0.05 late diastole compared with the middle or initial third) (Fig. 4). In contrast, greater filling occurred in the final two thirds of diastole in preoperative patients with ischemic heart disease: Group I 27, 36 and 37 percent and Group II 29, 35 and 36 percent (P <0.05 middle or last third compared with the first third). Postoperatively, the filling pattern in patients in Group I shifted toward normal with relatively more filling taking place in the early and middle portions and less in the final third compared with preoperative findings (P <0.05: 29, 41 and 30 percent) (Fig. 4). In contrast, the abnormal filling pattern in patients in Group II persisted postoperatively: 25, 34 and 41 percent (P >0.05 compared with preoperative values) (Fig. 4).

Discussion

This study demonstrates the relatively reversible nature of depressed left ventricular diastolic compliance in ischemic heart disease by restoration of coronary blood flow (Fig. 2 to 4). Since diminished left ventricular distensibility may result in increased pulmonary venous pressure,[15–18] improvement in abnormal ventricular passive pressure-volume relations may play an important role concomitant with enhanced contractile properties in the relief of congestive symptoms after myocardial revascularization. Although recent studies have demonstrated significant improvement in certain variables of left ventricular function after successful coronary artery bypass surgery,[1–3] there are no previous reports concerning the effects of this procedure on reduced left ventricular compliance in coronary artery disease.

Ventricular compliance in myocardial infarction and ischemia: Left ventricular compliance is reduced with the onset of myocardial ischemia.[11,19] Although compliance may increase in the early hours immediately after myocardial infarction as a result of tissue disruption and stress relaxation,[11] the ventricle then stiffens during the first few days, manifesting myocardial edema and fibrocellular infiltration in the healing stage.[11,12,20] Patients with chronic stable coronary artery disease also have a significant reduction in left ventricular distensibility[14–18] with the degree of compliance disorder related to the severity of coronary disease, previous myocardial infarction and the extent of abnormal segmental contraction.[14] Although changes in ventricular compliance related to ischemia have not previously been documented to be correctable in patients, alterations in left ventricular compliance associated with chronic volume overload may be at least partially reversible in some conditions as shown in children after closure of a ventricular septal defect[21] and in certain patients after surgical correction of aortic regurgitation.[22] In the latter condition, only patients with a nearly normal contractile state preoperatively had improvement of the

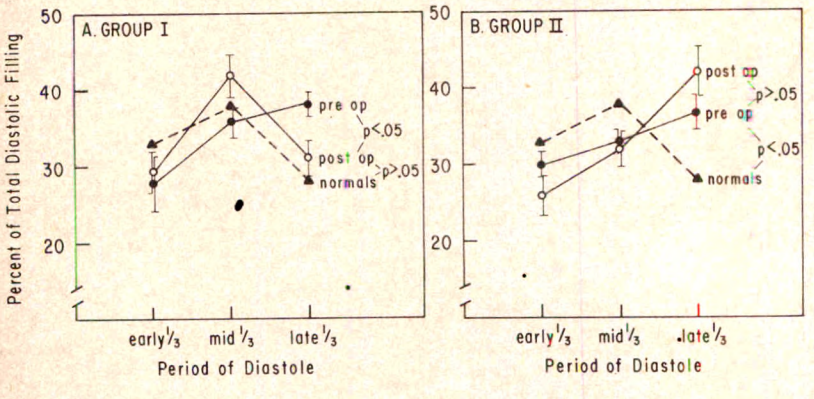

FIGURE 4. Effects of coronary artery bypass surgery on fractional left ventricular diastolic filling. The percents of total filling during three equal successive portions of diastole are indicated for patients with patent grafts (panel **A**) and occluded grafts (panel **B**) preoperatively (**closed circles** and **solid lines**) and postoperatively (**open circles** and **solid lines**). The filling pattern of eight normal patients is indicated by the **closed triangles** and **broken lines.** The **vertical bars** indicate standard error of the mean.

disturbed ventricular diastolic pressure-circumference curve.[22] Further, experimental studies have shown a progressive return toward normal of left ventricular diastolic compliance after correction of left ventricular volume overloading of a few weeks' duration.[23]

Factors influencing left ventricular compliance after coronary bypass: Several factors are known to influence the ventricular diastolic pressure-volume relation. Thus, left ventricular compliance may be altered by inherent chamber size, ventricular diastolic volumes, hypertrophy and wall thickness, ventricular geometry, frequency of contraction and the ventricular filling rate[10–12,17,24,25] as well as by left ventricular stiffness. Since there were no changes in end-diastolic volume, heart size, left ventricular mass, wall width, heart rate or filling rate postoperatively in the patients with patent bypass grafts (Group I), it is concluded that the improved left ventricular compliance in these patients was the result of reduction of ventricular stiffness. Further, the two groups of patients with coronary disease had similar values for each of these variables both before and after operation. In addition, the total observed diastolic compliance index was normalized for initial ventricular volume in each patient.[8,9] Further, the passive elastic modulus is a sensitive and specific left ventricular sitffness index that is independent of ventricular diastolic volume and pressure and nearly uninfluenced by variations in ventricular geometry.[10–12] From all of these observations, the increase in total functional diastolic compliance (Fig. 2), decrease in passive elastic modulus (Fig. 3) and improvement in the sequential filling pattern (Fig. 4) of the left ventricle in the patients with patent bypass grafts are interpreted to be due to decline of elevated left ventricular wall stiffness consequent to improved perfusion of areas of myocardial ischemia.

Ventricular compliance and contractility: Consistent with the increase in compliance in patients with patent bypass grafts was the improvement in ejection fraction (Fig. 1), and presumably contractile state, in these patients in contrast to those with occluded grafts, whose compliance indexes and ejection fraction were not altered. Since contractility itself does not directly affect ventricular compliance,[26] the concomitant enhancement of compliance and contractility in patients whose left anterior descending coronary artery bypass graft remained patent is most likely the result of revascularization of ischemic myocardium.

Role of preoperative or intercurrent myocardial infarction: Compliance was more reduced preoperatively in patients with than in those without myocardial infarction (Fig. 2 and 3). Further, in the group with patent grafts, the improvement in indexes of left ventricular diastolic compliance was principally accounted for by patients without myocardial infarction (Fig. 2 and 3). Thus, in eight patients in Group I with patent grafts and no transmural necrosis, total left ventricular observed compliance (Fig. 2) and passive elastic modulus (Fig. 3) improved markedly, whereas there was little or no change in compliance indexes in the remaining seven patients in Group I with preoperative or intercurrent myocardial infarction. Since previous myocardial infarction denotes a chronic left ventricular segmental scar[27] with marked stiffness, as shown by in vitro studies of surgically resected aneurysms,[28] it would not be anticipated that the severely reduced passive compliance of the fibrous area would be reversible. In addition, when these aneurysmal segments are extensive by electrocardiographic and angiographic assessment, the extent of improvement in total left ventricular diastolic compliance appears to be limited even when coronary blood flow is restored to potentially viable ischemic areas of myocardium.

Ventricular compliance and temporal pattern of ventricular filling: Previous studies[13,14] have demonstrated significant alterations in the normal temporal pattern of ventricular filling determined by sequential diastolic volume measurements in patients with severe chronic coronary artery disease, aortic stenosis and mitral insufficiency.[13,14] Normally, filling is greater in the early and middle portions of diastole,[13,14] as was also noted in our normal patients. In contrast, our patients with coronary disease manifested greatest filling in the final third of diastole, a finding consistent with results of previous studies in our laboratories[14] and by other workers.[13] Our present study shows that myocardial revascularization with an attendant increase in left ventricular compliance normalizes this abnormal pattern of ventricular filling characteristic of patients with ischemic heart disease (Fig. 4). Thus, in patients with patent grafts, the sequence of left ventricular filling returned toward normal with the most rapid filling taking place in the initial portions of ventricular diastole.

In contrast to patients with patent grafts, those with occluded grafts demonstrated an increase in late diastolic filling although, like the slight postoperative depressions in the other compliance indexes and in ejection fraction observed in these patients, the change was not significant ($P > 0.05$) (Fig. 4). It appears, therefore, that bypass occlusion tends to result in mild diminutions of left ventricular distensibility and cardiac function which probably are of little clinical consequence unless accompanied by concurrent myocardial infarction.

Clinical implications: This investigation has demonstrated by several expressions of diastolic compliance favorable alterations in left ventricular passive distensibility in patients with coronary disease and patent aortocoronary bypass grafts or internal mammary to left anterior descending coronary artery anastomoses. In such patients without previous myocardial infarction, a patent left anterior descending coronary artery bypass graft returns reduced compliance to normal, whereas increased ventricular stiffness is little affected by an open graft in patients with preoperative or intercurrent transmural infarction. This evidence of improvement in a sig-

nificant index of left ventricular integrity after successful myocardial revascularization affords further support for the physiologic value of coronary bypass procedures in properly selected patients.

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Mechanism of the Bradycardia During Coronary Angiography

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Bradycardia occurring during coronary angiography may be due to the direct effect of dye or to reflex vagal effects on pacemaker centers. Fifteen patients were classified according to the origin of the sinus nodal and atrioventricular nodal arteries. In patients with type A anatomy, both the sinus and the atrioventricular nodal arteries arose from the right coronary artery. In those with type B anatomy, only the atrioventricular nodal artery arose from the right coronary artery. Heart rate recordings were made during coronary angiography before and after selective infusion of atropine (0.2 mg) into the right coronary artery.

In type A patients, the sinus bradycardia observed during right coronary dye injection was caused by a combination of both direct and reflex effects on pacemaker tissue. Sinus bradycardia occurring with left coronary dye injections was entirely reflex in nature and was completely blocked with right coronary arterial injection of atropine.

In type B patients, sinus bradycardia with right coronary dye injections was produced by reflex suppression of the sinus pacemaker. A junctional rhythm was consistently produced after administration of atropine. Junctional bradycardia in type B patients was caused by direct suppression of the junctional pacemaker. Thus, angiographic dye appears to decrease heart rate both by a direct effect on pacemaker tissue and by reflex vagal suppression of the sinus pacemaker.

The injection of angiographic dye into the coronary arteries causes transient electrocardiographic and hemodynamic changes.[1–6] These changes include bradycardia, hypotension, depression of first derivative of left ventricular pressure (dP/dt),[2,4] prolongation of the P–R interval,[5,6] widening of the QRS complex,[6] marked repolarization changes[3] and a shift in the electrical axis.[3] Coronary angiographers have observed various degrees of bradycardia induced by dye injections into normal, abnormal and obstructed coronary arteries. The bradycardia is said to be eliminated by intravenous administration of atropine.[4–6] Some authors have speculated that the explanation for the bradycardia lies within the confines of two major areas: (1) an ischemic or physical effect of the dye upon pacemaker tissue,[1,2,7,8] or (2) a reflex vagal effect.[4–6] This study seeks to ascertain the mechanism of the bradycardia in man by correlating heart rate response with blood supply to the sinus and atrioventricular nodes. Before and after selective infusion of atropine into the right coronary artery, recordings of heart rate were made as angiographic dye was injected into the right and occasionally the left coronary arteries.

Materials and Methods

Twenty-five patients undergoing selective coronary angiography were studied for heart rate response. All studies were performed as part of the daily schedule of cardiac catheterization and coronary angiography (using the Sones technique) in patients with suspected heart disease. Nembutal®,

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100 mg, and atropine, 0.5 mg, were administered as premedication before the procedure. Heart rate recordings were made using an Electronics for Medicine photographic recorder (DR 12) at a paper speed of 50 mm/sec. The coronary injections were filmed with a 35 mm Arriflex camera at 80 frames/sec using a 5 inch image intensifier.

The films were examined to establish the origin of the sinus node and atrioventricular node arteries and to detect significant occlusive coronary disease. Patients with valvular disease, cardiomyopathy or congenital heart disease were excluded. Patients with greater than 50 percent obstruction of the coronary arteries were excluded with the exception of one patient who had a normal right coronary artery but 70 percent obstruction in the left anterior descending branch distal to the origin of the first septal artery. Ventricular function studies included determination of the first derivative of left ventricular pressure (dP/dt) and left ventricular end-diastolic pressure and performance of left ventricular cineangiography. The results were normal in all included cases.

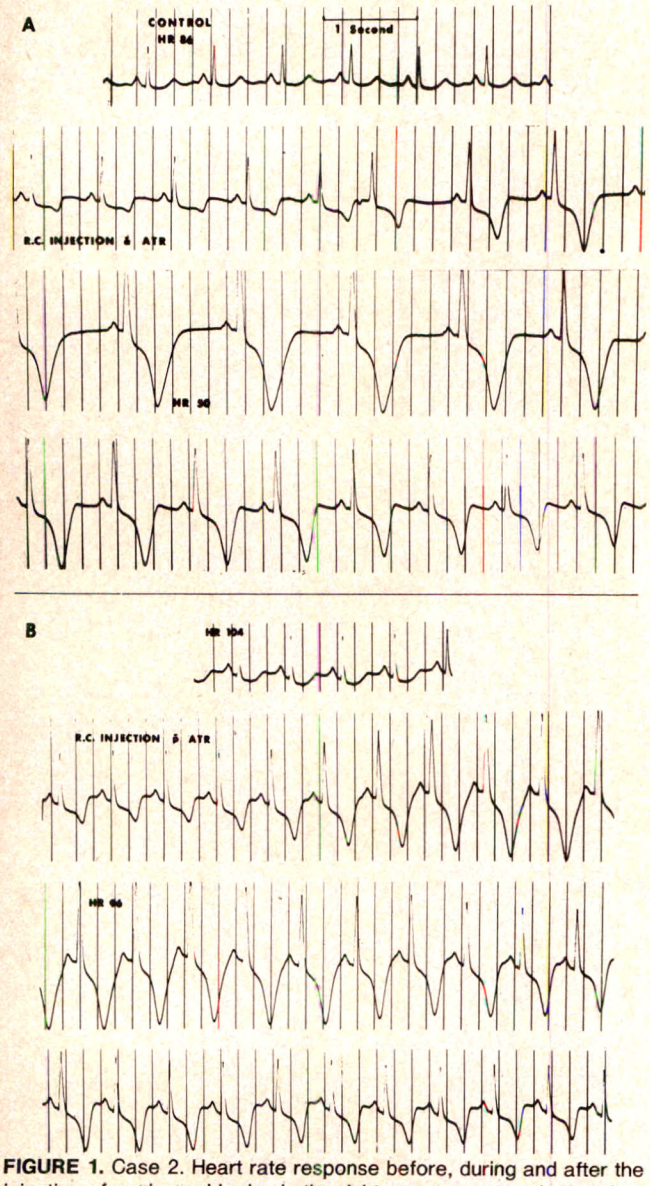

FIGURE 1. Case 2. Heart rate response before, during and after the injection of angiographic dye in the right coronary artery in a patient with type A anatomy. S-T and T wave changes provide evidence of maximal dye effect. **A,** before selective right coronary arterial injection of atropine. The control heart rate of 86 decreased to 50 beats/min during the dye injection, then gradually returned to normal. The sinus pacemaker maintained control throughout injection and recovery phases. This tracing demonstrates the occurrence of sinus bradycardia but does not identify direct or reflex effects. The three lower strips are continuous. **B,** after selective right coronary arterial injection of atropine there was sinus tachycardia with a control heart rate of 104 beats/min. A decrease in heart rate to 96 beats/min occurred during the dye injection. This response, since reflex effects were blocked, was due to direct depression of pacemaker discharge by angiographic dye. The three lower strips are continuous.

Patients were classified into two types on the basis of the blood supply to both the sinus and atrioventricular nodes. In type A, the blood supply to both nodes originated from the right coronary artery. In type B, the sinus nodal artery came from the circumflex branch whereas the right coronary artery gave rise to the atrioventricular nodal artery. Three major groups were studied.

Group I: Fifteen patients, 10 classified as type A and 5 as type B, were studied by recording the heart rate during the infusion of dye into the right coronary artery before and after selective right coronary arterial injection of atropine. The atropine, 0.2 mg in 10 cc of normal saline solution, was infused slowly into the right coronary artery after the appropriate control heart rate recordings had been made. Heart rate response immediately after the infusion was also recorded. In 2 of these 15 patients, both classified as type A, heart rate recordings were made during left coronary arterial injections before and after right coronary arterial infusion of atropine. There were nine men in the group, ranging in age from 36 to 60 years (mean age 50), and six women with an age range of 44 to 52 years (mean age 49).

Group II: Five patients were studied during the infusion of 8 to 10 ml of autogenous blood into the right coronary artery. This procedure was used to determine whether distension of the right coronary or the sinus nodal artery by the pressure of the injections contributed to the bradycardia.[9] All five patients were type A, with the sinus nodal artery originating from the proximal right coronary artery. This group did not undergo selective right coronary arterial injection of atropine.

Group III: Five patients, all type A, had heart rate recordings made during left coronary injections. None had selective right coronary arterial injections of atropine. All five patients, plus the two from Group I who received right coronary arterial injections of atropine, underwent evaluation of left coronary arterial injections.

Results

Type A: The heart rate response to the injection of angiographic dye into the right coronary artery of type A patients before and after selective right coronary atropinization is shown in Table IA. Sinus bradycardia developed in all patients during the dye infusion, both before and after infusion of atropine. The selective infusion of atropine produced an immediate increase in heart rate averaging approximately 25 percent. The sinus pacemaker consistently maintained rhythmic control after atropine infusion in all type A cases. Before administration of atropine, the heart rate decreased nearly 33 percent during the dye injection. After infusion of atropine, the heart rate during dye injection decreased approximately 17 percent. Atropinization did not completely eliminate cardiac slowing.

A typical example of the heart rate response in a type A patient is shown in Figure 1. Figure 1A demonstrates the effect on heart rate and electrocardiographic configuration before administration of atropine. The rhythm remains sinus with marked T wave inversion during maximal effect of the dye. The heart rate decreases from a control rate of 86 to 50 beats/min, then slowly returns to the control rate. Essentially the same effect is seen after administration of atropine (Fig. 1B), the only differences being a more rapid rate at the beginning of the infusion and a lesser degree of sinus bradycardia.

Type B: The results in patients with type B anatomy are shown in Table IB. Figure 2 illustrates the electrocardiographic changes in type B patients before and after administration of atropine. Certain similarities as well as significant differences between type A and B patients are apparent. First, before administration of atropine, sinus bradycardia developed in both types of patients during the infusion of dye (Fig. 1A and 2A). The magnitude of the bradycardia, 33 percent in type A and 24 percent in type B, was similar. Second, whereas an increase in sinus rate was always observed in type A patients after infusion of atropine, all type B patients manifested a junctional rhythm that was *always* faster than the control sinus rate (Table IB, Fig. 2B). Third, bradycardia did occur with dye infusion after administration of atropine in type B patients but with certain specific features. The junctional pacemaker maintained control of the rhythm past the point of maximal bradycardia. Episodes of isorhythmic atrioventricular dissociation frequently occurred during the recovery phase; maximal bradycardia usually occurred within 3 to 6 seconds after the infusion was begun (Fig. 2B). The junctional rate at the point of maximal slowing was less than the control sinus rate in all cases. However, the magnitude of the bradycardia was essentially the same before infusion of atropine (25 percent) as after the infusion (26 percent) in type B patients. This finding contrasts with observations in type A patients, whose heart rate after infusion of atropine was reduced from 33 to 17 percent.

The infusion of autogenous blood into the right coronary artery produced a mean decrease in heart rate of 2 percent in the five patients tested.

Left coronary injection of atropine: The decrease in heart rate during left coronary injections in the seven type A patients was 34 percent, almost identical to the decrease after right coronary injec-

TABLE I

Heart Rate Response After Injection of Angiographic Dye into the Right Coronary Artery

Case no.	Control Heart Rate (Sinus Rhythm) (beats/min)	Dye Injection Before Atropine: Change in Heart Rate (beats/min)	Dye Injection Before Atropine: % Decrease	Heart Rate Response and Rhythm After Selective Right Coronary Atropine: Change in Heart Rate (beats/min)	Heart Rate Response and Rhythm After Selective Right Coronary Atropine: % Increase	Heart Rate Response and Rhythm After Selective Right Coronary Atropine: Rhythm	Dye Injection After Atropine: Change in Heart Rate (beats/min)	Dye Injection After Atropine: % Decrease
A. Ten Patients with Type A Coronary Anatomy								
1	68	64–50	22	66–91	51	Sinus	86–73	18
2	100	96–66	31	91–124	36	Sinus	124–108	15
3	86	79–50	36	77–105	36	Sinus	104–96	8
4	88	88–69	21	86–94	10	Sinus	94–73	22
5	77	77–65	16	80–104	30	Sinus	104–88	16
6	110	110–66	40	110–130	18	Sinus	130–98	25
7	96	96–47	51	92–116	21	Sinus	116–94	20
8	79	82–50	39	80–83	3	Sinus	83–68	14
9	86	86–54	37	79–96	21	Sinus	96–70	26
10	77	77–50	35	65–91	40	Sinus	91–79	13
Mean	86.7 ±12.5	...	32.8 ±11.3	...	26.6 ±15.01	...	...	16.9 ±6.9
B. Five Patients with Type B Coronary Anatomy								
11	66	66–50	24	66–78	18	Junctional	78–57	19
12	83	83–65	15	78–104	25	Junctional	104–72	31
13	79	79–44	44	75–82	9	Junctional	82–51	38
14	71	71–69	4	68–74	10	Junctional	75–59	21
15	70	70–49	30	68–81	19	Junctional	81–65	21
Mean	72.8 ±7.0	...	23.8 ±12.2	...	16.2 ±6.0	...	...	26.0 ±7.3

A control heart rate (column 2) was recorded before any injection procedures were performed. Since right coronary injections came near the end of the procedure, the heart rate immediately before the right coronary injection (column 3) was sometimes slightly different from the original control heart rate. The same applies to the heart rate present at the time atropine was infused (column 5). Similarly, in column 8, the heart rate at the time of dye injection was slightly different from that achieved immediately after the infusion of atropine.

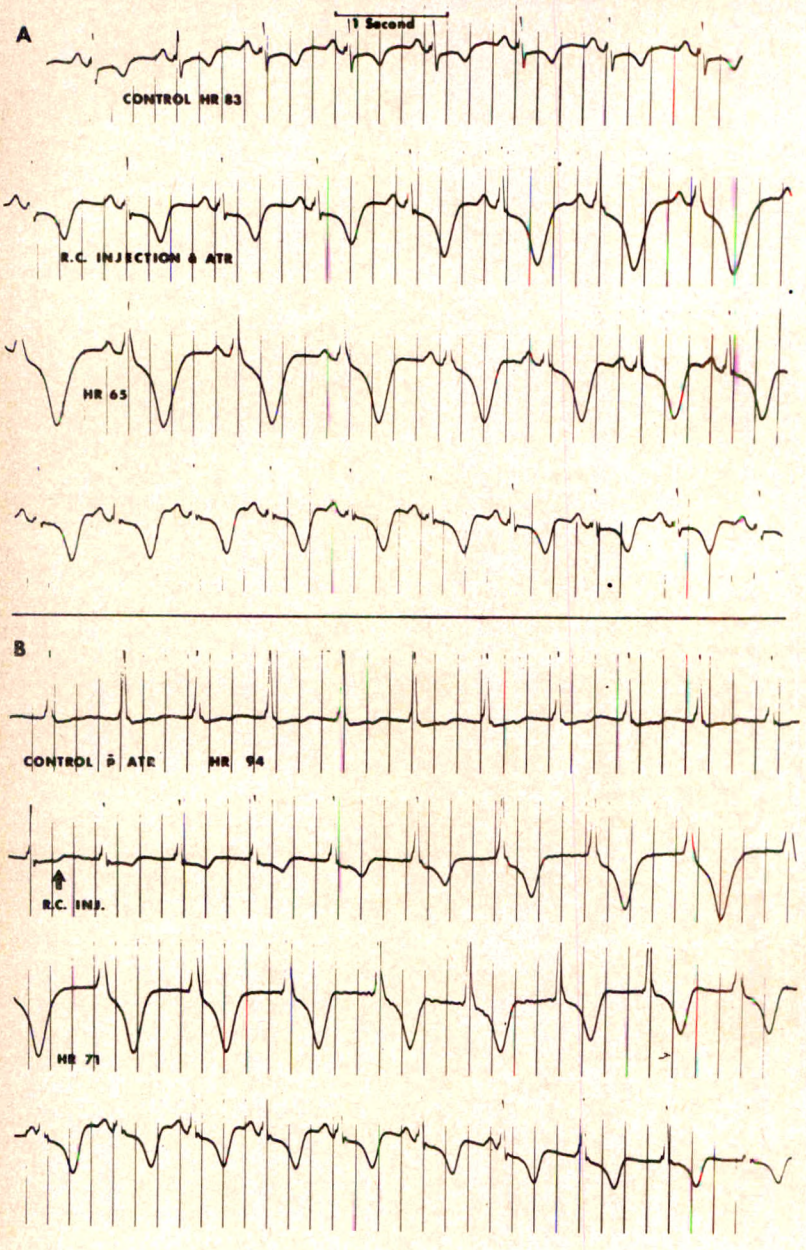

FIGURE 2. Patient 12. Heart rate response in type B patient after the infusion of angiographic dye into the right coronary artery. **A,** before selective right coronary injection of atropine. Note heart rate change (sinus bradycardia) from 83 to 65 beats/min, and the corresponding S-T wave changes due to maximal dye effect. Essentially the same response occurred in type A patients before injection of atropine. The three lower strips are continuous. **B,** after selective injection of atropine into the right coronary artery there was a stable junctional heart rate of 94 beats/min. A decrease in heart rate from 94 to 71 beats/min occurred during the dye infusion. The rhythm remained junctional past the point of maximal bradycardia. Isorhythmic atrioventricular dissociation occurred briefly **(bottom strip).** The three lower strips are continuous.

tion in these same patients. In the two type A patients tested both before and after right coronary injection of atropine, the bradycardia was completely eliminated by the cholinergic blockade.

Discussion

Under normal circumstances the sinus node is the primary pacemaker of the heart.[10] In abnormal physiologic conditions, the atrioventricular junctional region has been recognized as a secondary pacemaker center.[11] All factors that directly or indirectly influence these two centers of cardiac rhythm should be given utmost attention when considering chronotropic responses of the heart.

Mechanisms of Bradycardia After Dye Injection

In our attempt to explain the bradycardia following the injection of angiographic dye into the right coronary artery, there are two primary considerations: (1) the direct effects of the dye on pacemaker tissue, and (2) the reflex vagal effects on pacemaker discharge. For our purposes, any heart rate response believed to be due to the physical or chemical properties of the dye, including anoxia, is considered a direct effect on pacemaker tissue. The stimulation of neurogenic receptors by the angiographic dye, which subsequently affects heart rate indirectly, is considered a reflex effect.

Sinus nodal distension: The possible distension of the sinus nodal artery during the injection of dye is a secondary consideration. In dogs, such distension regularly produces transient bradycardia.[12] Although so far unproved, the same reponse may occur in man. Since the sinus nodal artery arises from the proximal right coronary artery in type A patients, distension could conceivably occur during the injection of dye

and contribute to the bradycardia. Our results, using autogenous blood instead of dye, demonstrate relatively little change, less than 5 percent, in heart rate. This response was not considered a significant factor in the production of the bradycardia.

Vagal effects on sinus and atrioventricular nodes: Autonomic reflexes, particularly those affecting the sinus and atrioventricular nodes, are important in the control of heart rate and rhythm.[13] Heavily concentrated areas of cholinergic nerve endings have been found in these regions and may be considered prime centers of reflex activity.[14] The dual cholinergic innervation of both sinus and atrioventricular nodes is a well known clinical and experimental fact.[13] We assume that reflex effects producing bradycardia are caused by the stimulation of vagal receptors, activating an afferent limb that travels by way of the vagus nerve to the central nervous system and subsequently back by the efferent limb to both the sinus and atrioventricular nodes. The resulting bradycardia is primarily produced by vagal effects on the sinus pacemaker. Vagal efferents may pass also to the atrioventricular nodal region, but the effects may not be evident because of the dominance of the sinus pacemaker.

Bezold-Jarisch effect on chemoreceptors: Receptors of various types have been identified in both the atria and ventricles of experimental animals.[15–18] A heavy concentration of receptors has been found in the region of the sinus and atrioventricular nodes.[15] Some of these receptors are stimulated by pressure changes and by chemical stimulation.[16] Chemical receptors have been found in the heart, primarily in the left ventricle of experimental animals,[18] which, when stimulated by various means, give rise to the Bezold-Jarisch effect or reflex.[18–22] This reflex response is characterized by both bradycardia and hypotension. The bradycardia produced by the injections of angiographic dye may be the human counterpart of the Bezold-Jarisch reflex. In our study, the types of receptors that were stimulated and their precise location are not known. Theoretically, if chemoreceptors are limited to the left ventricle and do respond to angiographic dye, a left coronary injection would be expected to stimulate them and produce reflex changes in heart rate. Our results with left coronary injections support this reasoning. Left coronary injections in type A patients produced the same degree of bradycardia as did right coronary injections, yet little or no dye circulated to the sinus or atrioventricular node. Elimination of the bradycardia in two of these patients by selective right coronary injection of atropine definitely suggests a reflex response. Firm conclusions on this point should not be drawn since only two patients were studied after right coronary injection, but other reasonable alternative explanations are lacking.

Right vs. left coronary arterial dye injection: The right coronary artery in all patients in this study supplied blood to at least a portion of the inferior wall of the left ventricle and inferior intraventricular septum. A right coronary injection may therefore be expected to circulate dye to and possibly stimulate any chemoreceptors located in the left ventricle. Thus, the heart rate response with a right as well as with a left coronary injection may reflect reflex suppression of pacemaker discharge. Since the volume of ventricular muscle supplied by the right coronary artery is considerably less than that supplied by the left coronary artery, the magnitude of the reflex response may be less with the right coronary injection. In our studies, this proved to be correct. The reflex effect of a left coronary injection was double that of a right coronary injection in type A patients.

The intracardiac route of the Bezold-Jarisch reflex in dogs has been determined to be along the left coronary artery, exiting near the left coronary ostia.[20] This may be true also of the left coronary artery in man. Since the human right coronary artery supplies the inferior wall of the left ventricle in 90 percent of cases,[23] the possibility that afferents travel with the right coronary artery and exit from the heart near the right coronary atria should be considered.

Response in Type A Patients to Right Coronary Injections

Heart rate response was quite consistent in that sinus bradycardia was produced by each right coronary injection (Fig. 1A). Since the dye circulated to both the sinus and atrioventricular nodes, the bradycardia may have been caused by direct or reflex effects, or both.[24] Deciding which effect was operative was aided by cholinergic blockade of both sinus nodal and atrioventricular junctional regions by selective right coronary injection of atropine. The production of sinus tachycardia (an average of 26.6 percent increase in heart rate) indicates, we believe, effective vagal blockade of at least the sinus pacemaker. This blockade did not interfere with pacemaker dominance, nor did it eliminate the bradycardia during right coronary injections (Fig. 1B). This result would not have occurred if the bradycardia operated entirely by reflex. We believe the bradycardia in type A patients during a right coronary injection is the result of both reflex and direct effects, each contributing equally to the bradycardia.

Response in Type B Patients to Right Coronary Injections

We interpret the consistent production of a junctional rhythm rather than a sinus tachycardia after right coronary injection of atropine as concrete evidence of a separate blood supply to the sinus and atrioventricular nodal regions in type B patients. A right coronary injection in this instance is considered a selective atrioventricular nodal infusion maneuver. In man this is as close as one can come to a selective atrioventricular nodal arterial injection.[25] The heart rate response must be interpreted in light of this anatomic difference between type A and B patients.

Heart rate response before atropine: The infusion of dye produced a sinus bradycardia very similar to that seen in type A patients (Fig. 1A and 2A). The

mechanism of the bradycardia cannot be the same because dye does not circulate to the sinus node: Direct depressant effects of dye on the sinus pacemaker therefore cannot explain the bradycardia. The only possible explanation for the slowing of sinus nodal discharge is reflex suppression. Direct conduction across the free atrial wall would occur much too slowly to produce these effects. The reflex must originate with receptors located in the distribution of the right coronary artery, and the reflex effect must occur very quickly since the sinus pacemaker remains in control throughout injection and recovery. Atrioventricular dissociation did not occur.

Heart rate response after atropine: The major response to this maneuver was a shift in the dominant pacemaker from the sinus nodal to the atrioventricular junctional region, with an increase in the heart rate (Fig. 2B). The cholinergic blockade of all efferent nerves surrounding the junctional pacer prevented any reflex change in heart rate. Any change in the firing rate of this junctional pacemaker could have been due only to the direct effects of the dye. The receptors and afferent nerves were not blocked nor were any efferent nerves to the sinus node blocked. The infusion of dye into the right coronary artery produced a junctional bradycardia of the same magnitude as that produced before infusion of atropine when the sinus node was the dominant pacemaker. These data lead us to believe that the bradycardia in type B patients, just as in type A, was due to a combination of both direct and reflex effects. In type A patients the two effects were additive, whereas in type B they were nonadditive but equal or equivalent. This may explain why the magnitude of the bradycardia was slightly less in type B than in type A patients before administration of atropine.

Before infusion of atropine, the discharge rate of the sinus pacemaker was suppressed entirely by reflex, masking any direct effects at the atrioventricular junction. After the infusion, the sinus pacemaker failed to emerge when the junctional rate fell below the control sinus rate during the maximal dye effect (Fig. 2B). This is the second piece of evidence indicating reflex suppression of sinus nodal function in type B patients.

A junctional heart rate, faster than the sinus rate, occurred after administration of atropine in type B patients (Fig. 2B). The observed firing rate of the junctional pacemaker in most clinical situations is reported to be between 40 to 60 beats/min[26] and is often referred to as the "inherent" firing rate of the atrioventricular junctional pacer. Our work suggests that the inherent firing rate of this pacemaker, free from vagal influence, may be faster than 40 to 60 beats/min. The evidence also implicates vagal efferent connections in relation to pacemaker dominance.

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H-V Interval in Patients with Bifascicular Block (Right Bundle Branch Block and Left Anterior Hemiblock)

Clinical, Electrocardiographic and Electrophysiologic Correlations

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Electrophysiologic studies were performed in 119 adults with chronic bifascicular block manifested by right bundle branch block and left anterior hemiblock. The H-V interval was normal in 86 patients and prolonged in 33. The following clinical variables were more frequent ($P < 0.05$) in patients with a prolonged H-V interval: cardiac third sound, mitral systolic murmur, cardiomegaly on chest roentgenogram, congestive heart failure and cardiac functional class III or IV (New York Heart Association criteria). The following differences in the electrocardiographic and electrophysiologic findings were found: Patients with a prolonged H-V interval had a longer mean P-R interval, QRS duration and A-H interval ($P < 0.02$). All patients were followed up prospectively in a cardiac conduction disease clinic after initial evaluation. The mean follow-up periods were (mean ± standard error of the mean) 514 ± 49 and 563 ± 34 days for the patients with a prolonged and normal H-V interval, respectively. Progression of conduction disease occurred in three patients (4 percent) with a normal H-V interval and in four (12 percent) with a prolonged interval. The cumulative 3 year mortality rate for the entire group was 25 percent. The patients with a prolonged H-V interval had a higher cumulative 2 year mortality rate than those with a normal H-V interval but the difference was not statistically significant. In summary, a prolonged H-V interval was often associated with serious myocardial dysfunction and a high mortality rate. The risk of progression of conduction disease was slight with either a prolonged or a normal H-V interval during this relatively short follow-up period.

The H-V interval is a measure of conduction time from His bundle depolarization to the onset of ventricular activation.[1,2] In patients with right bundle branch block and left anterior hemiblock, the H-V interval is a measure of conduction time in the His bundle and the posterior fascicles of the left bundle branch system. Prolongation of this interval in a patient with right bundle branch block and left anterior hemiblock should reflect the presence of conduction disease in the posterior fascicle or distal His bundle, or both. Pathologic studies suggest the presence of trifascicular disease in patients with bundle branch block and a prolonged H-V interval.[3] It is not known whether H-V prolongation in such a patient predicts a high risk of subsequent atrioventricular (A-V) block, Stokes-Adams attacks or sudden cardiac death.[4–7]

In this study we examined several clinical, electrocardiographic and electrophysiologic variables in patients with right bundle branch block and left anterior hemiblock with both normal and prolonged H–V intervals in an attempt to further define the significance of this interval. In addition, all patients studied were followed up prospectively in a cardiac conduction disease clinic. This report presents our detailed observations on the short-term prognostic significance of the H-V interval in these patients.

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Material and Methods

Patient Selection

Since February 1970, our laboratory has been engaged in a prospective study of patients with intraventricular conduction disease whose condition has been detected in the inpatient and outpatient facilities of the Cook County Hospital, the West Side Veterans Hospital and the University of Illinois Hospital, Chicago. Additional patients are referred to us for electrophysiologic studies and follow-up in our cardiac conduction clinics by private physicians in the greater Chicago area.

To be entered in the study, patients must give informed consent for electrophysiologic studies and must agree to be followed up in a cardiac conduction disease clinic. This report describes our findings in 119 adults (aged 18 or over) with chronic right bundle branch block and left axis deviation (mean axis more negative than −30°) whose condition was detected between February 1970 and August 1973 and who were followed up through June 1974. Patients who had second or third degree block before or at the time of study are excluded from this report.

Initial Evaluation

Electrophysiologic diagnosis: All patients were hospitalized upon entering the study. A complete history and physical examination were obtained by a cardiac fellow and reviewed by one of the senior authors. Serial electrocardiograms were obtained. The diagnosis of complete right bundle branch block and left anterior hemiblock was based on a modification of the criteria of Rosenbaum.[8] The following criteria were used: (1) QRS duration of 0.12 second or greater, (2) RSR or qR configuration of the QRS in lead V_1, and (3) left axis deviation with a mean frontal QRS axis more negative than −30°. QRS duration was defined as the longest QRS interval in the standard and augmented limb leads. The P-R interval was defined as the longest interval from the onset of the P wave to the onset of the QRS complex in the standard and augmented limb leads. Significant Q waves were defined by standard electrocardiographic criteria.[9]

Clinical diagnosis: On the basis of the history, physical examination, electrocardiogram, chest roentgenogram and laboratory findings, a clinical diagnosis was reached. Arteriosclerotic heart disease was diagnosed if the patient had (1) a history of exertional chest pain suggestive of angina pectoris, or (2) a previous diagnosis of definite myocardial infarction, or both. Hypertension was diagnosed if two or more blood pressure recordings indicated a systolic pressure greater than 140 mm Hg and diastolic pressure greater than 90 mm Hg. Patients with both arteriosclerotic and hypertensive heart disease were classified for analysis as patients with arteriosclerotic heart disease. Valvular heart disease was diagnosed when a significant valvular lesion could be detected by auscultation or cardiac catheterization, or both. Primary myocardial disease was diagnosed if cardiomegaly (on routine posteroanterior chest roentgenogram, using cardiothoracic ratio) was present without demonstrable cause. Primary conduction disease was diagnosed if heart size was normal and there was no evidence of organic heart disease, with the exception of intraventricular conduction defect. Third and fourth heart sounds were diagnosed by auscultation.

His bundle electrocardiogram: Cardiac drugs were withheld for at least 48 hours before the initial study. His bundle electrograms were recorded by previously described catheter techniques[1,10] at the time of each patient's entry into the study. Refractory periods were measured with the atrial extrastimulus technique, as previously reported.[11] The following intervals were measured: (1) P-A (mean ± 2 standard deviations; normal 27 ± 18 msec), from the onset of the P wave on the surface electrocardiogram to the onset of the first high frequency potential of the low atrial electrogram recorded by the His bundle catheter. This interval reflected conduction time from the high to the low right atrium. (2) A-H (normal 92 ± 38 msec), from the first high frequency potential of the low atrial electrogram to the first high frequency potential of the His bundle electrogram. This interval reflected A-V nodal conduction time. (3) H-V (normal 43 ± 12 msec), from the first high frequency potential of the His frequency potential of the His electrogram to the earliest deflection of the QRS complex detected on multiple surface leads. The measurements were made at a paper speed of 200 mm/sec and reflect the average of 10 consecutive beats. Atrial pacing was used to validate H potentials.[12]

Patient Follow-Up

All patients were prospectively followed-up in a conduction clinic at intervals of 1 to 2 months after the initial study, or at shorter intervals if clinically indicated. Clinic examinations consisted of a history, physical examination and a 12 lead electrocardiogram. Portable tape recorder monitoring of electrocardiograms was used in symptomatic patients for detection of transient bradyarrhythmias. Patients who missed appointments were followed up by mail, telephone or house call if necessary. When patients moved from Chicago, electrocardiograms and data from clinical evaluations were obtained from local physicians. No patient was lost to follow-up during the study period. If death occurred outside the hospital, details of the death as well as a copy of the death certificate was obtained. Deaths were classified as either sudden or not sudden. Sudden death was defined as unexpected death occurring instantaneously or within an estimated 3 hours of the onset of acute symptoms.

Analysis of Data

All information obtained during initial evaluation and subsequent visits was keypunched and stored on disk (IRS database system). Specifically designed programs were used for data recall. Statistical analysis was performed with use of a Biomedical Statistical Program (BMD × 76). Standard t test was used for testing the significance of differences in means. In a contingency table of 2 × 2, the chi-square method with Yates correction for continuity was used for frequency data analysis. Survival data were analyzed by previously described life table methods.[13,14]

Results

Clinical data: On the basis of the initial electrophysiologic study, the 119 patients were separated into two groups: (1) 86 patients had a normal H-V interval (31 to 55 msec) and are referred to as the normal H-V group. (2) 33 patients had a prolonged H-V interval (56 to 100 msec) and are referred to as the prolonged H-V group. The age and sex distribution of both groups are presented in Table I.

The mean age ± standard error of the mean was 61.9 ± 1.8 years for the normal H-V group and 62.6 ± 2.9 years for the prolonged H-V group of patients. The difference was not statistically significant (NS, P

TABLE I

Age and Sex Distribution of 119 Patients with Right Bundle Branch Block and Left Anterior Hemiblock

Age Group (yr)	Normal H-V (86 patients)		Prolonged H-V (33 patients)	
	no.	Sex	no.	Sex
18–20	1	1M, 0F	1	1M, 0F
21–30	6	6M, 0F	0	0M, 0F
31–40	2	1M, 1F	2	2M, 0F
41–50	6	5M, 1F	3	3M, 0F
51–60	20	15M, 5F	5	4M, 1F
61–70	24	17M, 7F	9	4M, 5F
71–80	18	15M, 3F	12	10M, 2F
81–90	8	6M, 2F	1	1M, 0F
91–100	1	1M, 0F	0	0M, 0F

>0.10). There were 57 men and 19 women in the normal H-V group and 25 men and 8 women in the prolonged H-V group (NS).

The clinical classification of heart disease in the 119 patients is presented in Table II. There was no significant difference in the prevalence of different types of disease between normal and prolonged H-V groups.

Symptoms and physical findings: The frequency of cardiovascular symptoms and selected historical findings are presented in Table III. There was a greater prevalence of dyspnea (P <0.1), New York Heart Association cardiac functional classes III and IV (P <0.001) and congestive heart failure (P <0.01) in the group with a prolonged H-V interval. The frequency of selected physical and radiologic findings is presented in Table IV. A mitral systolic murmur (P <0.01), protodiastolic gallop (P <0.02) and cardiomegaly on chest roentgenogram (P <0.05) occurred more frequently in the prolonged than in the normal H-V group.

Electrocardiographic data (Table V): P-R intervals and QRS durations were significantly greater in the prolonged H-V group (P <0.001 and <0.01) than in the normal H-V group. There was no significant difference in regard to frontal QRS axis or the presence or absence of Q waves. Premature ventricular contractions, detected on the resting 12 lead electrocardiogram, were more common in the prolonged H-V group although the difference was not statistically significant.

Despite the longer P-R and QRS intervals in the prolonged H-V group, these measurements were of little value in predicting H-V duration. Twenty-five patients had P-R prolongation (>0.20 second); 12 of these were in the normal and 13 in the prolonged H-V group. Forty-three patients had a QRS duration of 0.16 second or greater; 29 of these were in the normal and 14 in the prolonged H-V group.

Electrophysiologic data: Conduction intervals and other electrophysiologic data are presented in Table VI. Only the A-H interval was significantly longer in the prolonged H-V group (P <0.02). Block

TABLE II

Classification of Heart Disease in 119 Patients with Right Bundle Branch Block and Left Atrial Hemiblock

Classification of Heart Disease	Normal H-V (86 patients)		Prolonged H-V (33 patients)		
	no.	%	no.	%	P
Hypertensive	33	38	9	27	NS
Arteriosclerotic	22	26	11	34	NS
Valvular	1	1	2	6	NS
Primary myocardial disease	3	3	3	9	NS
Primary conduction disease	23	27	4	12	NS
Other	4	5	4	12	NS

NS = not significant; P = probability.

TABLE III

Cardiac Symptoms and Selected Historical Findings in 119 Patients with Right Bundle Branch Block and Left Anterior Hemiblock

Symptoms	Normal H-V (86 patients)		Prolonged H-V (33 patients)		
	no.	%	no.	%	P
Dizziness	29	34	9	27	NS
Syncope	9	11	3	9	NS
Angina	12	14	6	18	NS
Dyspnea	27	31	17	52	<0.10
NYHA class					
I–II	83	97	24	73	<0.001
III–IV	3	3	9	27	<0.001
Congestive heart failure	19	22	16	49	<0.01
Previous myocardial infarction	11	13	5	15	NS
Diabetes mellitus	13	15	10	30	NS

NYHA class = New York Heart Association functional classification.

TABLE IV

Selected Physical and Chest Roentgenographic Findings in 119 Patients with Right Bundle Branch Block and Left Anterior Hemiblock

	Normal H-V (86 patients)		Prolonged H-V (33 patients)		
	no.	%	no.	%	P
Systolic murmur, mitral area	11	13	12	36	<0.01
Protodiastolic gallop (S3)	5	6	8	24	<0.02
Atrial gallop (S4)	48	56	21	64	NS
Cardiomegaly on chest roentgenogram	41	48	24	72	<0.05

TABLE V

Electrocardiographic Findings in 119 Patients with Right Bundle Branch Block and Left Anterior Hemiblock

	Normal H-V (86 patients)			Prolonged H-V (33 patients)			
		Patients			Patients		
	Mean ± SEM	no.	%	Mean ± SEM	no.	%	P
P-R interval (sec)	0.177 ± 0.003	...	...	0.21 ± 0.002	...	...	<0.001
QRS duration (sec)	0.141 ± 0.002	...	...	0.149 ± 0.003	...	...	<0.01
QRS axis (degrees)	−67.27 ± 2.62	...	...	−73.64 ± 5.29	...	...	NS
Significant Q waves	...	35	41	...	17	52	NS
Atrial fibrillation	...	3	3.5	...	0	0	NS
Ventricular premature complexes	...	10	12	...	6	18	NS

SEM = standard error of the mean.

TABLE VI

Conduction Times and Refractory Periods in 119 Patients with Right Bundle Branch Block and Left Anterior Hemiblock

	Normal H-V		Prolonged H-V		
	Mean ± SEM	no. of patients	Mean ± SEM	no. of patients	P
P-A (msec)	29.82 ± 1.17	83	31.36 ± 2.09	33	NS
A-H (msec)	100.18 ± 2.89	83	113.40 ± 7.02	33	<0.02
Atrial ERP (msec)	264.12 ± 6.58	40	267.50 ± 14.60	18	NS
A-V nodal ERP (msec)	360.40 ± 10.39	25	343.18 ± 15.78	11	NS
HPS ERP (msec)	402.50 ± 17.5	2	472.50 ± 52.52	2	NS
SA nodal recovery time (msec)	984.79 ± 26.98	64	1041.6 ± 56.30	30	NS

ERP = effective refractory period; HPS = His-Purkinje system; SA = sinoatrial.

distal to the His potential during atrial pacing occurred in two patients in the normal H-V group (at paced heart rates of 100/min and 171/min, respectively) and in two patients from the prolonged H-V group (at paced heart rates of 140 and 180/min, respectively). None of these patients had progression of conduction disease during the follow-up period.

Follow-up data: The mean follow-up periods for the normal and prolonged H-V groups were (mean ± standard error of the mean) 563 ± 34 and 514 ± 49 days, respectively. The total cumulative 3 year mortality rates and mortality rates due to sudden death in all the patients studied are presented in Table VII and Figure 1. Four of the patients who died suddenly had arteriosclerotic heart disease. The cumulative 3 year mortality rates, comparing the normal and prolonged H-V groups, are shown in Table VIII and Figure 2. The prolonged H-V group had a higher mortality rate at 2 and 3 years, but the differences were not statistically significant. The 2 year cumulative mortality for sudden death was similar in the normal and prolonged H-V groups.

Twenty-two of the 119 patients died, 14 in the normal H-V group (6 suddenly) and 8 in the prolonged H-V group (2 suddenly). The 14 patients who did not die suddenly died of congestive heart failure or cardiogenic shock, or both (7 patients), pneumonia (3 patients), cerebrovascular accident (1 patient), postoperative complications (2 patients) and bronchogenic carcinoma (1 patient).

Progression of conduction disease: In three patients (4 percent) with a normal H-V interval, second or third degree A-V block developed: in one, at an unknown site, secondary to transient hyperkalemia (on day 6 after entry into the study); in one, distal to the His potential, without precipitating cause (on day 2); and in one, at an unknown site, detected during portable tape recorder monitoring (on day 17).

In four patients (12 percent) with a prolonged H-V interval, second or third degree block developed: in one, distal to the His potential, secondary to acute anteroseptal infarction (on day 351); in one, at an undetermined site, after cardiac surgery (on day 58); and in one, proximal to the His potential, without precipitating cause (on day 71); and in one, proximal to the His potential, secondary to digitalis (on day 136). Idiopathic progression of conduction disease occurred in only three patients, two with a normal and one with a prolonged H-V interval.

Discussion

The H-V interval in patients with right bundle branch block and left anterior hemiblock is a measure of conduction time in the His bundle and posterior fascicles of the left bundle branch system. Pathologic studies in a limited number of cases suggest that

TABLE VII

Cumulative Mortality Rate for 119 Patients with Right Bundle Branch Block and Left Anterior Hemiblock

	Mortality Rate ± Standard Error (%)	Patients Exposed to Risk of Dying (no.)
Total mortality		
1st year	14 ± 3	112
2nd year	21 ± 4	63
3rd year	25 ± 6	19
Mortality due to sudden death		
1st year	6 ± 2	107
2nd year	9 ± 3	62
3rd year	9 ± 3	19

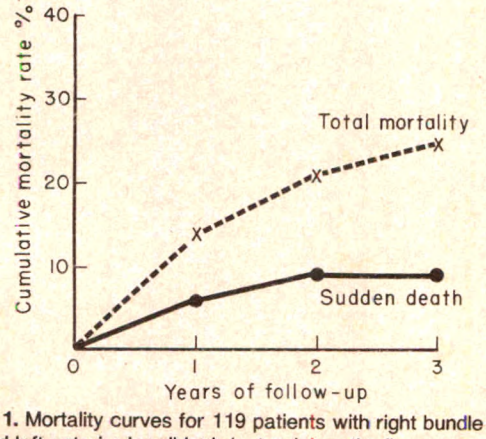

FIGURE 1. Mortality curves for 119 patients with right bundle branch block and left anterior hemiblock (actuarial method) representing the yearly cumulative mortality rates after His bundle study from sudden and nonsudden deaths combined (x– – –x) and from sudden death alone (•——•).

TABLE VIII

Comparative Cumulative Mortality Rates of the Normal and Prolonged H-V Groups

	Normal H-V (86 patients)		Prolonged H-V (33 patients)		
	Mortality Rate ± Standard Error (%)	Patients Exposed to Risk of Dying (no.)	Mortality Rate ± Standard Error (%)	Patients Exposed to Risk of Dying (no.)	*P*
Total mortality					
1st year	14 ± 4	80	16 ± 6	32	NS
2nd year	18 ± 5	46	30 ± 9	18	NS
3rd year	23 ± 7	16	30 ± 9	9	NS
Mortality due to sudden death					
1st year	7 ± 3	77	3 ± 3	30	NS
2nd year	8 ± 3	45	9 ± 6	17	NS
3rd year	8 ± 3	15	9 ± 6	4	NS

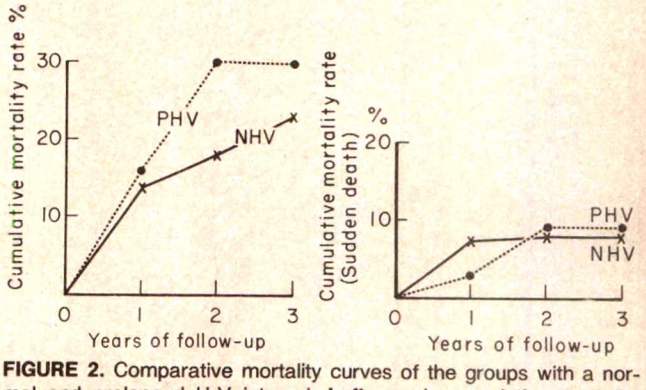

FIGURE 2. Comparative mortality curves of the groups with a normal and prolonged H-V interval. **Left,** yearly cumulative mortality rates. **Right,** yearly cumulative mortality rates from sudden death. NHV (x——x) = normal H-V interval; PHV (•– – –•) = prolonged H-V interval.

a prolonged H-V interval in these patients reflects the presence of trifascicular conduction disease.[3,15] The reported incidence of a prolonged H-V interval (>55 msec) in patients with right bundle branch block and left anterior hemiblock ranges from 17 to 50 percent.[4,7,16,17] In the study by Narula et al.,[4] 31 of 68 patients with this conduction defect had an H-V interval greater than 55 msec. In our study 36 percent of patients had a prolonged H-V interval.

Clinical, Electrocardiographic and Electrophysiologic Correlations

In our series, a prolonged H-V interval was associated with a significantly increased prevalence of signs and symptoms of myocardial dysfunction, such as dyspnea, apical systolic murmurs, third heart sound, cardiomegaly and congestive heart failure. This was surprising in view of the pathologic studies of Lenegre[18] and Lev,[19] who suggested that the most common pathologic process responsible for bilateral bundle branch disease (trifascicular disease) was primary sclerodegenerative disease involving the cardiac skeleton and the intraventricular conduction system. However, neither of these workers excluded the presence of additional organic heart disease or other etiologic mechanisms for the production of bilateral bundle branch block.

Several mechanisms may explain the high incidence of myocardial dysfunction in the patients with a prolonged H-V interval: (1) The same disease process, arteriosclerotic or hypertensive, for example, directly involves both the working myocardium and the conduction system. (2) The same etiologic factors are responsible for both sclerodegenerative bilateral bundle branch disease and ventricular muscle disease. (3) The prolonged H-V interval in patients with bifascicular block may reflect stretch of the left ventricle, in a manner similar to that in which incomplete right bundle branch block occurs in patients with diastolic overload of the right ventricle.

We believe there is a significant prevalence of undiagnosed trifascicular disease in the normal H-V group (Lev's disease, Lenegre's disease), which has not produced H-V prolongation. This possibility is supported by the spontaneous occurrence of block distal to the His potential in patients with bundle branch block and a normal H-V interval.

Although P-R intervals and QRS durations were significantly longer in the prolonged H-V group, these findings alone or in combination had little value in predicting the H-V interval. This observation was in contrast to results of a previously reported study[5] in patients with left bundle branch block, in which a P-R interval greater than 0.20 second in combination with a QRS duration greater than 0.16 second predicted H-V prolongation.

The prevalence of a prolonged A-H interval was significantly greater in the prolonged H-V group, suggesting an association of A-V nodal and intraventricular conduction disease that contributed to the frequent P-R prolongation found in this group. There was no significant difference in intraatrial conduction time (P-A interval), or atrial and A-V nodal effective refractory periods in the groups with a normal and prolonged H-V interval. The number of patients whose effective refractory period of the His-Purkinje system was determined was too small to permit a conclusion to be reached.

Follow-Up (Natural History)

The progression of bifascicular block to complete heart block has been demonstrated in previous studies.[8,17,20–23] The reported incidence of development of heart block in patients with right bundle branch block and left anterior hemiblock ranges from 6 to 30 percent over a period of several months to several decades. All previous reported studies concerning progression of bifascicular block have been retrospective. The present study is the first prospective study on the natural history of these patients. Documented progression of conduction disease was uncommon, occurring in only 6 percent of patients during a mean follow-up period of approximately 1 1/2 years. Surprisingly, the site of A-V block was not always distal to the His bundle. The risk of progression of conduction disease was similar in both the prolonged and normal H-V groups during the relatively short follow-up period.

Mortality

The cumulative mortality rate in our total group of patients with bifascicular block was high, being 14 percent in the 1st year, 21 percent in the 2nd year, and 25 percent in the 3rd year. These statistics were similar to those reported by DePasquale and Bruno,[23] who noted a 23 percent mortality rate with a follow-up period ranging from 0 to 15 years.

In this series, the patients with a prolonged H-V interval had a greater cumulative mortality. This observation appears to reflect the higher incidence of myocardial disease in this group, most of these patients dying of cardiac failure. Patients in both the normal and prolonged H-V groups had a relatively high incidence of sudden cardiac death. Sudden death in both groups of patients could reflect either progression of conduction disease or ventricular fibrillation. We believe the latter to be a frequent causative mechanism of sudden death in our patients. A recent report[24] revealed a high rate of ventricular arrhythmias manifested in the electrocardiograms of patients with intraventricular conduction defects. Also, in our study patients in both the normal and prolonged H-V groups had a high incidence of ventricular premature beats. In addition, we recently reported[25] that the majority of patients with bifascicular block, when subjected to graded treadmill exercise, manifested premature beats and, occasionally, ventricular tachycardia. However, sudden death due to asystole secondary to progression of intraventricular conduction disease cannot be excluded in either of our two groups of patients.

Therapeutic Implications

Our data do not allow us to recommend prophylactic pacing in patients with right bundle branch block and left anterior hemiblock and either a normal or a prolonged H-V interval. We emphasize that the mean follow-up period in this prospective series was approximately 1 1/2 years and that, with continued study, it may be possible to delineate a group with significant risk of progression of conduction disease.

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Subendocardial Ischemia Provoked by Tachycardia in Conscious Dogs with Coronary Stenosis

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We investigated the effect that mild coronary stenosis exerts on the ability of the coronary circulation to compensate for the increased extravascular compression that occurs in the subendocardium during tachycardia. An electromagnetic flowmeter transducer and balloon cuff occluder were implanted on the left circumflex coronary artery in seven dogs, and experiments were performed 1 week later with the dogs under sedation but conscious. Stenosis of the left circumflex artery was produced by partial inflation of the cuff occluder. We determined coronary blood flow distribution by the radioactive microsphere technique, injecting 200,000 15μ spheres into the left ventricular cavity during (1) a control period, (2) stenosis of the left circumflex artery and a normal heart rate, and (3) stenosis of the left circumflex artery and tachycardia. When the heart rate was normal, the degree of stenosis used caused no change in myocardial microsphere distribution but eliminated postocclusion reactive hyperemia. Thus, reserve coronary vasodilation compensated for the stenosis. With the degree of stenosis kept constant, an increase in heart rate to 196 beats/min caused a marked transmural shift in distribution of microspheres from subendocardium into subepicardium within the region of the left ventricle supplied by the left circumflex artery. There was no significant transmural shift in the region supplied by the uninvolved left anterior descending coronary artery. Myocardial lactate extraction decreased. These results suggest that when reserve coronary vasodilation has already been utilized to compensate for coronary stenosis, the increased extravascular coronary compression from tachycardia causes subendocardial ischemia and hypoxia.

Myocardial contraction increases the resistance to coronary blood flow during systole by compressing intramyocardial blood vessels. Since compression is greater in the subendocardial (inner) than in the subepicardial (outer) layer of the left ventricle,[1,2] an increase in frequency of contraction could be expected to shift coronary blood flow from the inner to the outer layer of the left ventricular muscle. In previous experiments employing the radioactive microsphere technique, we found that in conscious dogs with normal coronary circulation, tachycardia did cause a slight relative transmural shift in microsphere distribution from the inner to the outer layer.[3] This change was slight enough to suggest that coronary vasodilation during tachycardia nearly compensated for the increased subendocardial compression of coronary blood vessels.

Patients with coronary artery disease who have partly expended their reserve coronary vasodilation to meet myocardial nutritional needs even under basal conditions would be less capable of additional coronary vasomotor compensation. In these patients, tachycardia might cause a more pronounced transmural shift in coronary blood flow, resulting in subendocardial hypoxia.

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The purpose of this study was to determine the effect of tachycardia on coronary blood flow distribution when reserve coronary vasodilation already had been partially exploited in compensating for coronary stenosis. Tachycardia was induced in dogs with isolated stenosis of the left circumflex coronary artery. We compared the changes in transmural microsphere distribution in the regions of the left ventricle supplied by the stenosed left circumflex and by the normal left anterior descending coronary arteries.

Methods

Experimental Preparation

A left thoracotomy was performed in seven mongrel dogs weighing 20 to 35 kg. Anesthesia was induced by inhalation of halothane. A segment of the proximal left circumflex coronary artery was dissected and encircled with a Statham electromagnetic flowmeter transducer, 2.0 or 2.5 mm in diameter. A balloon cuff occluder containing mercury was secured around the artery about 5 mm distal to the transducer. There were no intervening arterial branches between the transducer and the occluder. The proximal connections of the flowmeter transducer and cuff occluder were positioned subcutaneously on the dog's back, and the chest was closed.

The experiment was performed 5 to 10 days later with the animal awake and breathing spontaneously. Acepromazine (Ayerst), 1 mg/kg body weight intravenously, and morphine, 30 mg intramuscularly, were administered for sedation, and 2 percent lidocaine was used for local skin analgesia. The flowmeter and cuff occluder connections were retrieved through a skin incision in the dog's back, and catheters were inserted through neck vessels and positioned under fluoroscopy in the coronary sinus, left ventricle and aortic arch. A dose of 2,000 units of heparin was administered.

Observations were made (1) during control conditions, (2) at the resting heart rate 10 to 15 minutes after producing stenosis of the left circumflex coronary artery, and (3) after 10 to 15 minutes of tachycardia, keeping the degree of stenosis of the left circumflex artery constant. The stenosis was achieved by introducing enough mercury into the cuff occluder tubing to reduce the left circumflex flowmeter mean flow rate by approximately 20 percent. The degree to which the vessel lumen was narrowed is unknown. To induce tachycardia, we administered atropine intravenously by increments of 0.1 mg until a heart rate of approximately 200 beats/min was reached (0.6 to 1.2 mg of atropine). In previous experiments, tachycardia induced by atropine or atrial pacing produced comparable changes in microsphere distribution, thus indicating that atropine itself had no specific effect on coronary blood flow distribution.[3]

Observations

Lead II of the electrocardiogram and pressures in the aorta and left ventricle, sensed by P23Gb Statham transducers, were recorded on a Brush Mark 200 ink writer.

Paired aortic and coronary venous blood samples were obtained for determination of partial pressure of oxygen (PO_2) and pH (Radiometer), hemoglobin (cyanmethemoglobin) and lactate concentrations. Blood oxygen concentration was calculated from PO_2, pH and hemoglobin concentration, assuming a normal oxygen dissociation curve.

Flowmeter transducers were calibrated in vitro using dog blood at 38° C. To determine zero blood flow during experiments, we temporarily occluded the left circumflex coronary artery. Changes in the available reserve coronary vasodilation were evaluated from the reactive hyperemia response that followed 10 seconds of left circumflex occlusion. During the control period, temporary occlusion of the left circumflex artery was achieved by introducing mercury into the cuff occluder tubing. During stenosis, temporary occlusion was achieved by manually compressing the exposed tubing, rather than by adding mercury into the tubing. In this way, when the compression was released, the original degree of stenosis returned.

Microsphere Techniques

The distribution of coronary blood flow was determined by the microsphere technique, our use of which has been described.[3] The spheres (3M Co.) were 15 μ in diameter and labeled with either ^{85}strontium, ^{141}cesium, or ^{95}niobium, used in random sequence. For each determination, approximately 200,000 microspheres were introduced into the left ventricular catheter over a 15 second period.

After completion of the experiment, the dog was killed by intravenous injection of pentobarbital. To compare distribution of coronary blood flow in ischemic and normally perfused myocardium, we divided the left ventricle into portions supplied by the left circumflex coronary artery and by the left anterior descending coronary artery. We cut the free wall of the left ventricle into three regions based on the distribution of its visible epicardial arteries: (1) muscle supplied by the left circumflex coronary artery distal to the cuff occluder, (2) muscle supplied by the left anterior descending coronary artery, and (3) a marginal region apparently supplied mainly by the left anterior descending artery but adjacent to the muscle supplied by the left circumflex artery. The marginal region was about 1 cm wide and contained half the mass of the muscle supplied by the left circumflex artery. The interventricular septum was cut into three corresponding regions: (1) posterior zone, apparently mainly supplied by the left circumflex coronary artery, (2) anterior zone, apparently mainly supplied by the left anterior descending coronary artery, and (3) mid or marginal zone.

We cut each of these regions into blocks small enough to be sliced accurately into halves: inner and outer halves for the free wall and left and right halves for the septum. We considered the interventricular septum part of the left ventricle and, for convenience, termed its half facing the left ventricular cavity "inner" and its half facing the right ventricular cavity "outer." Samples were placed in 25 mm diameter glass tubes and weighed, and their radioactive emissions were counted in a Nuclear Chicago 1185 series automatic gamma counting system, calibrated using ^{137}cesium as a standard before each run.

Calculations and Statistics

Mean coronary blood flow (ml/g · min) (Table I) was calculated from the left circumflex coronary arterial flowmeter reading (ml/min) divided by the weight (g) of the left ventricular free wall and septal regions supplied by the left circumflex coronary artery. Calculation of the relative regional distribution of coronary blood flow depended only on relative data on counts per minute (gamma emission counts/min attributable to the isotope administered, although for ease of expression the results may be expressed as relative microsphere concentrations). The fraction of the left ventricular coronary blood flow to any region (Table II) was calculated from the counts per minute of that region divided by the counts per minute of the total left ventricle. The ratio of coronary blood flow per gram between inner and outer layers of any region (transmural distribution,

TABLE I

Hemodynamic Data (mean ± standard error of the mean)

	Control	LC Stenosis	LC Stenosis & Tachycardia
Heart rate (beats/min)	82 ± 8.6	90 ± 9.8	196 ± 8.6†
Aortic blood pressure (mm Hg)			
Systolic	117 ± 4.1	114 ± 3.4	107 ± 3.8
Diastolic	78 ± 2.9	78 ± 2.8	83 ± 6.1
Mean	90 ± 2.8	90 ± 2.4	91 ± 5.7
LVEDP (mm Hg)	6 ± 1.4	5 ± 0.61	1 ± 0.73*
LC CF (ml/g·min)	0.58 ± 0.073	(0.46 ± 0.057†)	(0.57 ± 0.073)

* = $P<0.05$; † = $P<0.01$ (significance of difference from control).
CF = coronary blood flow; LC = left circumflex coronary artery; LVEDP = left ventricular end-diastolic pressure.
Parentheses enclosing the LC CF data serve to emphasize that the values during stenosis and during tachycardia represent blood flow through the transducer only and do not include blood flow into the circumflex system by way of collateral routes.

TABLE II

Regional Distribution of Microspheres (mean ± standard error of the mean)

Region	Percent LV Weight	Percent of LV Microspheres		
		Control	LC Stenosis	LC Stenosis & Tachycardia
LV free wall				
LAD	21.3 ± 1.3	21.8 ± 1.1	21.0 ± 1.3	23.6 ± 1.8
Marginal	11.6 ± 1.1	12.0 ± 1.4	11.8 ± 1.1	11.9 ± 0.98
LC	24.7 ± 1.1	24.5 ± 1.4	24.8 ± 0.98	18.0 ± 2.3†
Septum				
LAD	19.1 ± 1.2	18.5 ± 1.7	18.8 ± 1.3	20.9 ± 1.8*
Marginal	11.4 ± 1.2	11.8 ± 1.2	11.5 ± 1.2	13.6 ± 0.82*
LC	11.9 ± 0.61	11.4 ± 0.69	12.2 ± 0.57	11.9 ± 0.78
LV total	100.0	100.0	100.1	99.9

* $P<0.05$; † $P<0.01$ (significance of difference from control).
LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LV = left ventricular.

TABLE III

Transmural Distribution of Microspheres (I/O Ratio) (mean ± standard error of the mean)

Region	Control	LC Stenosis	LC Stenosis & Tachycardia
LV free wall			
LAD	1.28 ± 0.045	1.32 ± 0.025	1.20 ± 0.045
Marginal	1.41 ± 0.15	1.32 ± 0.090	1.04 ± 0.11*
LC	1.31 ± 0.078	1.15 ± 0.094	0.67 ± 0.086†§
Septum			
LAD	1.32 ± 0.065	1.30 ± 0.057	1.28 ± 0.090
Marginal	1.23 ± 0.082	1.23 ± 0.078	1.11 ± 0.078‡
LC	1.31 ± 0.082	1.28 ± 0.041	0.95 ± 0.073†‡

* $P<0.05$; † = $P<0.01$ (significance of difference from control).
‡ $P<0.05$; § $P<0.01$ (significance of difference from left anterior descending coronary artery).
Abbreviations as in Table II.

Table III) was calculated from the value of counts per minute per gram for the inner layer divided by this value for the outer layer.

Statistical significance was judged by a two-tailed paired t test.

Results

Hemodynamic data (Table I): Mean control left circumflex coronary arterial blood flow determined from the flowmeter transducer was 0.58 ml/g · min. Left circumflex coronary arterial stenosis decreased the mean left circumflex flowmeter reading to 0.46 ml/g · min but caused no significant change in the other variables listed. The stenosis produced no change in lead II of the electrocardiogram. An increase in heart rate to 196 beats/min (mean) during left circumflex coronary arterial stenosis decreased the left ventricular end-diastolic pressure in each dog but caused no consistent change in left circumflex coronary blood flow or other variables.

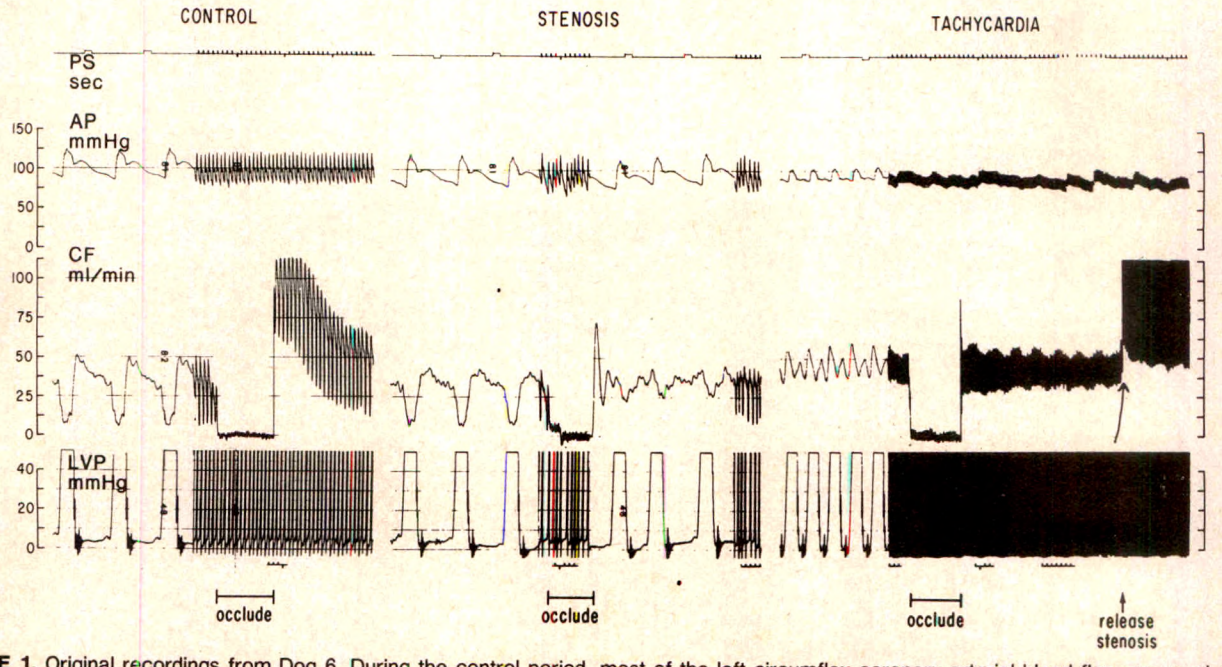

FIGURE 1. Original recordings from Dog 6. During the control period, most of the left circumflex coronary arterial blood flow occurred during diastole, and a 10 second period of left circumflex occlusion was followed by reactive hyperemia. Stenosis of the left circumflex coronary artery decreased mean blood flow in this artery from 31 to 27 ml/min and produced very little change in the flowmeter tracing contour. The hyperemia that followed a 10 second period of complete occlusion of the left circumflex artery was markedly attenuated. The fast paper speed tracing immediately after release of the occlusion reveals a relative increase in left circumflex blood flow during systole, which disappeared within a few heartbeats, as illustrated in the slow paper speed tracing. The temporary increase in systolic coronary blood flow after the occlusion could have been due to a transient reduction in contractile force and extravascular compression in the myocardium supplied by the left circumflex artery, consistent with results of beta adrenergic inhibition.[4] Tachycardia increased mean blood flow in the left circumflex artery to 49 ml/min. There was very little postocclusion reactive hyperemia during tachycardia in the presence of the stenosis, however, and the marked increase in left circumflex blood flow after release of the stenosis during tachycardia indicates that left circumflex blood flow would have increased to more than 49 ml/min if the stenosis had not been present. AP = aortic pressure; CF = left circumflex coronary blood flow; LVP = left ventricular pressure; PS = paper speed with 1 second time marks.

Flowmeter tracings for a single experiment illustrated in Figure 1 are representative also of the other experiments in the features to be described, unless indicated otherwise. During the control period, 10 seconds of left circumflex coronary arterial occlusion was followed by reactive hyperemia. Left circumflex coronary arterial stenosis caused only a slight decrease in left circumflex coronary blood flow but essentially obliterated the postocclusion reactive hyperemia. There were no significant changes in aortic or left ventricular end-diastolic blood pressures during stenosis. In this experiment, tachycardia during stenosis caused a slight increase in left circumflex coronary arterial blood flow, but in three of the seven experiments tachycardia decreased blood flow in this artery. During tachycardia, there was essentially no reactive hyperemia response after a 10 second occlusion of the left circumflex coronary artery. Release of the stenosis by removing mercury from the cuff occluder during tachycardia caused a pronounced increase in left circumflex coronary arterial blood flow.

Left circumflex vs. left anterior descending coronary arterial flow: The relative distribution of microspheres between regions of the left ventricle supplied by the left circumflex and left anterior descending coronary arteries is presented in Table II. During the control period, the percent of total left ventricular microspheres trapped in each region was proportional to the relative weight of the region; that is, the concentration of microspheres per gram was essentially uniform. Left circumflex coronary arterial stenosis exerted no significant effect on microsphere distribution. However, tachycardia during left circumflex coronary arterial stenosis decreased the percent of microspheres received by the left ventricular free wall region supplied by the left circumflex coronary artery and increased the percent of microspheres received by the interventricular septal region supplied by the left anterior descending coronary artery.

The decrease in left circumflex coronary arterial flowmeter reading combined with unaltered microsphere distribution during left circumflex arterial stenosis during a normal heart rate suggests that the regions initially supplied by the left circumflex coronary artery were now supplied partly by this artery and partly by collateral blood flow. The appearance of collateral blood flow was verified by a single experiment (Fig. 2) in which a slight decrease in left circumflex coronary arterial blood flow caused by local stenosis caused a prompt reciprocal increase in blood flow in the left anterior descending coronary artery.

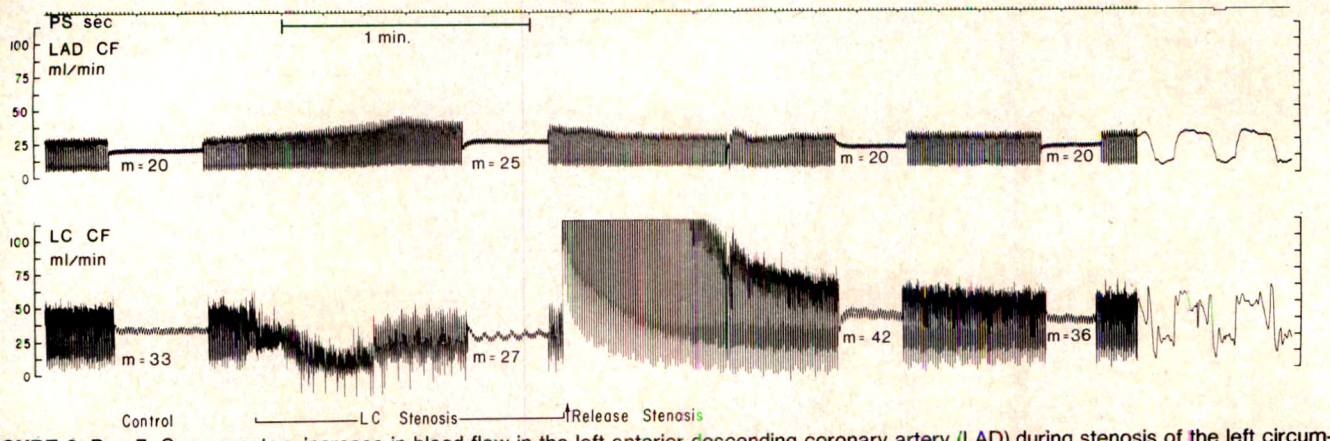

FIGURE 2. Dog 7. Compensatory increase in blood flow in the left anterior descending coronary artery (LAD) during stenosis of the left circumflex coronary artery (LC). The increase in coronary blood flow (CF) in the left anterior descending artery was detectable within a few seconds. Release of the stenosis was followed by reactive hyperemia in the left circumflex artery and return of blood flow in the left anterior descending artery to its initial value. The reciprocal increase in blood flow in the left anterior descending artery during left circumflex stenosis represents collateral blood flow to the myocardial region originally supplied by the left circumflex artery. m = mean; PS = paper speed.

Inner vs. outer transmural distribution of flow: The transmural distribution of spheres between inner and outer layers of the left ventricular wall (I/O ratio) is presented in Table III. Control I/O values were greater than unity, as shown previously in conscious dogs with a normal heart rate,[3] and were not different in regions supplied by the left circumflex and left anterior descending coronary arteries. Left circumflex coronary arterial stenosis caused no significant change in the I/O ratio for any region. Tachycardia during left circumflex coronary arterial stenosis caused marked decreases in the I/O ratio in the free wall and septal regions supplied by that artery. There was no significant change in I/O ratio in regions supplied by the left anterior descending coronary artery, and there were intermediate decreases in this ratio in the marginal regions of the free wall and septum.

Metabolic data: The effects of left circumflex coronary arterial stenosis and tachycardia on metabolic data are presented in Table IV. There were no significant changes in arterial or coronary venous blood oxygen concentration or PO_2. Myocardial lactate extraction ratio (L[a-v/a]) was unaffected by the left circumflex coronary arterial stenosis but decreased during tachycardia in six of the seven dogs, and in one dog lactate uptake reversed to lactate production. The mean decrease in L(a-v/a) during tachycardia was approximately 50 percent ($0.05 < P < 0.1$).

TABLE IV

Metabolic Data (mean ± standard error of the mean)

	Control	LC Stenosis*	LC Stenosis & Tachycardia*
CaO_2 (ml/100 ml)	17.4 ± 0.30	17.8 ± 0.31	17.4 ± 0.53
$C(a\text{-}v)O_2$ (ml/100 ml)	11.4 ± 1.1	12.9 ± 0.49	12.3 ± 0.53
PaO_2 (mm Hg)	71.9 ± 2.2	71.3 ± 4.1	68.5 ± 4.6
PvO_2 (mm Hg)	22.1 ± 2.4	19.4 ± 1.4	20.4 ± 1.3
L(a-v/a)	0.42 ± 0.045	0.47 ± 0.073	0.22 ± 0.11

* Significance of difference from control $P < 0.05$ for all variables.

a = arterial; C = concentration; L = lactate; P = partial pressure; v = coronary venous.

Discussion

Previous studies[5–7] have established that coronary ischemia itself, if of sufficient magnitude, causes a transmural shift in coronary blood flow distribution. Marked reduction in left main coronary arterial blood flow in open chest dogs with isolated and controlled coronary perfusion[5,6] or complete occlusion of the left circumflex branch by an implanted snare in closed chest dogs[7] produced relatively more severe ischemia in the inner than in the outer layer of the left ventricle. The authors of these studies postulated that when reserve coronary vasodilation was utilized to compensate for the low level of distal coronary perfusion pressure, coronary blood flow was more dependent upon the transmural gradient of intramyocardial tissue pressure surrounding the coronary vessels. In other experiments,[8] a similar shift in transmural coronary blood flow away from the inner or subendocardial layer was provoked by systemic hemodynamic interventions that decreased coronary diastolic perfusion pressure relative to left ventricular systolic pressure.

Transmural coronary blood flow distribution during tachycardia: Our experiments were designed to determine the effect of tachycardia on distribution of transmural coronary blood flow in the presence of relatively mild coronary stenosis, that is, to evaluate the influence that the coronary vasomotor adjustment to the stenosis exerted on the ability of the coronary circulation to adjust further to the metabolic and mechanical consequences of tachycardia. We wished to simulate conditions in the patient

whose coronary circulation is compensated under basal resting conditions but who is subject to myocardial hypoxia when the myocardial nutritional needs for coronary blood flow and the intramyocardial coronary vascular compression both increase during tachycardia. Stenosis of the left circumflex coronary artery in our dogs initially had no effect on the left ventricular regional or transmural distribution of microspheres, thus indicating that the stenosis by itself was well compensated as long as the heart rate remained under basal conditions. The compensation appears to have involved at least two mechanisms: (1) coronary arteriolar dilation distal to the stenosis, as implied by the elimination of postocclusion reactive hyperemia, and (2) collateral blood flow into the myocardium initially supplied by the left circumflex coronary artery, as implied by the decrease in left circumflex flowmeter reading combined with unaltered microsphere distribution. An alternative explanation for the decrease in left circumflex coronary arterial blood flow and normal microsphere distribution would be a uniform decrease in coronary blood flow (and myocardial oxygen consumption) for the entire left ventricle due to focal left circumflex coronary arterial stenosis. Although we directly documented the increase in collateral contribution from the left anterior descending coronary artery in only one experiment, the alternative explanation seems untenable, especially in the absence of deterioration of left ventricular function or appearance of myocardial anaerobic metabolism. Other investigators[9,10] have presented evidence that in dogs the left anterior coronary artery provides collateral blood flow to the distal left circumflex coronary artery immediately after sudden complete occlusion of the proximal left circumflex coronary artery.

Although the left circumflex coronary arterial stenosis exerted no effect on coronary blood flow distribution, the loss of postocclusion reactive hyperemia (Fig. 1) suggested that coronary vasodilation initially available for compensation was at least partly expended even with the heart rate at low basal levels. Reserve vasodilation was not necessarily completely exhausted. For example, the left circumflex coronary arterial blood flow subsequently increased slightly during tachycardia in some of the dogs. In any case, with a reduction in reserve vasomotion, the coronary circulation distal to the left circumflex coronary stenosis was more susceptible to the mechanical effects of tachycardia on intramyocardial coronary blood vessels. Since extravascular compression from contraction was more marked in the subendocardium, the I/O ratio in the myocardial tissue supplied by the stenosed left circumflex coronary artery was reduced during tachycardia. The decrease in the I/O ratio occurred in the septal as well as the free wall regions of the left ventricle supplied by the left circumflex coronary artery.

In the previous experiments in dogs with normal coronary arteries,[3] an increase in mean heart rate from 73 to 193 beats/min caused a slight but definite decrease in I/O ratio throughout all regions of the left ventricle (mean I/O ratio decreased from 1.29 to 1.11, $P < 0.01$). In the present experiments, when heart rate was increased to a comparable degree, the decrease in I/O ratio in the myocardium supplied by the normal left anterior descending coronary artery was smaller and not statistically significant. Although it seems likely that this discrepancy was related to the left circumflex coronary arterial stenosis, we have no specific satisfactory explanation for it. If the left circumflex coronary arterial stenosis drained collateral blood from the normal left anterior descending coronary arterial region, one might expect the decrease in I/O ratio in this region during tachycardia in the dogs with left circumflex stenosis to be greater, not less than normal.

The experimental model studied by Flameng et al.[11] is relevant to our investigation. They showed that tachycardia combined with pharmacologically induced diffuse coronary vasodilation caused a shift in microsphere distribution from inner to outer layers of the region of the left ventricle supplied only by collateral blood flow. Although they attributed the microsphere redistribution to "coronary steal" into the normally perfused myocardium, the results are consistent as well with extravascular compression in a region where compensatory reserve coronary vasodilation has been expended.

Transmural metabolic effects of ischemia during tachycardia: Transmural metabolic effects of coronary ischemia have been studied by others. Sudden complete occlusion of the left anterior descending coronary artery[12] or a gross reduction in left main coronary arterial blood flow[13] produced increases in myocardial lactate concentration that were greater in the inner than in the outer layer of the ischemic myocardium. A lesser degree of coronary constriction produced no significant myocardial metabolic effects, presumably because of compensatory coronary vasodilation but, as in our experiments, rendered the subendocardium susceptible to subsequent superimposed vasomotor adjustment requirements. Under these conditions, administration of isoproterenol, which caused only slight metabolic effects in dogs with normal coronary circulation, provoked a marked lactate concentration gradient from subendocardium to subepicardium.[14] When blood flow to the entire left coronary system was compromised, the increased myocardial lactate concentration was accompanied by increased lactate concentration and decreased oxygen concentration in coronary sinus blood.

For analysis of the metabolic consequences of the focal subendocardial ischemia in our experiments, we are limited to interpretation of changes in arterial and coronary sinus blood oxygen and lactate concentrations. The coronary L(a-v/a) decreased in all but one dog, but there was no corresponding consistent decrease in coronary sinus blood oxygen concentration, in contrast to findings in the experiments with constriction of the left main coronary artery. The same combination of decreased L(a-v/a) without de-

creased coronary sinus blood oxygen concentration frequently occurs when angina pectoris is induced by tachycardia in patients with ischemic coronary artery disease.[15–18] It seems likely that the inconsistency of the changes in coronary sinus blood oxygen concentration that occur when myocardial hypoxia is induced by tachycardia in patients and in dogs with focal coronary stenosis is related to a combination of factors including (1) the heterogeneous nature of coronary sinus blood, which represents a capricious mixture of coronary venous blood from ischemic and relatively normal perfused myocardium, and (2) a systematic redistribution of blood flow, with a larger share through the subepicardium where the tissue PO_2 level is apparently higher.[19]

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Effects of Unipolar Cathodal and Bipolar Stimulation on Vulnerability of Ischemic Ventricles to Fibrillation

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The effects of unipolar and bipolar stimulation on ventricular fibrillation threshold were studied during acute occlusion of the left anterior descending coronary artery in 13 anesthetized dogs. Values for ventricular fibrillation threshold were determined by delivering trains of rapid bipolar or unipolar pulses (100/sec) during the vulnerable period. The mean threshold value was found to be 13.0 ma for bipolar, 13.9 ma for unipolar anodal and 21.0 ma for unipolar cathodal stimulation. Ventricular fibrillation threshold was significantly lower ($P < 0.01$) with both unipolar anodal and bipolar stimulation than with unipolar cathodal stimulation. In these animals, the first premature beats induced by the rapid stimuli occurred significantly earlier with unipolar anodal and bipolar stimulation than with unipolar cathodal stimulation.

The effect of competition of unipolar or bipolar pacing stimuli with normally conducted ventricular beats was also studied in a group of 16 dogs. Repeated trials of competitive pacing during coronary occlusion showed that the incidence of ventricular fibrillation was significantly greater ($P < 0.05$) with bipolar pacing (36 percent) than with unipolar cathodal pacing (15 percent). These results indicate that bipolar pacing is potentially more dangerous than unipolar cathodal pacing and suggest that the incidence of pacemaker-induced ventricular fibrillation might be further reduced by the use of unipolar cathodal stimulation during acute myocardial infarction.

Both unipolar cathodal and bipolar electrode systems are used for permanent ventricular pacing with implanted pacemakers, but virtually all temporary ventricular pacing is currently performed with a bipolar pacemaker system. The possibility that ventricular fibrillation will be induced by a pacemaker stimulus falling in the vulnerable period exists when a fixed-rate pacemaker competes with spontaneously occurring beats.[1–6] This risk is even greater in patients whose ventricle is paced during acute myocardial infarction.[4–8] The use of demand or standby pacemakers has reduced the possibility of pacemaker-induced ventricular fibrillation,[2] but these pacemakers are not totally safe, since they may fail to sense spontaneous beats and continue to function in the fixed-rate mode.[9] A recent report[10] suggests that the elimination of bipolar pacing systems may further reduce the frequency of ventricular fibrillation induced by the competitive pacing.[10]

The risk of ventricular fibrillation had not been considered to be dependent upon the type of pacing stimuli until Preston[10] reported recently that all documented cases of pacemaker-induced ventricular tachycardia or fibrillation occurred in association with bipolar stimulation. It might be argued whether this single report is sufficient evidence for eliminating the bipolar pacing system since it is possible that cases of ventricular tachyarrhythmias induced by unipolar cathodal stimulation may have been overlooked. In view of the clinical importance of this matter, we examined the effects of unipolar and bipolar stimulation on ventricular vulnerability to fibrillation during acute myocardial ischemia.

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Methods

Mongrel dogs weighing 10 to 20 kg were anesthetized by intravenous injection of sodium pentobarbitol, 30 to 35 mg/kg body weight. Under artificial respiration, a midline thoracotomy was performed and the heart was cradled in the opened pericardium. The sinoatrial node was inactivated by crushing in order to drive the heart at a constant rate by stimuli applied to the right atrium or ventricle. A femoral artery was cannulated to obtain arterial samples for the determination of blood gas and to monitor arterial pressure. Arterial blood gas and pH levels were frequently checked and corrected as necessary. For reversible occlusion of the anterior descending branch of the left coronary artery, the artery was dissected free 15 to 20 mm from its origin, and a snare was applied around the vessel. The artery was occluded about 5 minutes before each determination of ventricular fibrillation threshold.

The bipolar stimulating and recording electrodes were small steel hooks with an interelectrode distance of about 5 mm. The stimulating electrodes were attached to the anterior septal margin of the right ventricle about 10 mm from the edge of the area of expected ischemia. The recording electrodes were attached to a site close to the stimulating electrodes. For unipolar stimulation, cathodal or anodal stimuli were delivered through one of the pair of stimulating electrodes, and a hypodermic needle inserted subcutaneously in the right front leg served as the indifferent electrode. A lead III electrocardiogram, the local electrogram and the artifact of stimuli delivered to the stimulating electrodes were recorded on an Electronics for Medicine recorder or a Grass polygraph recorder. The stimuli were also displayed on an oscilloscope and calibrated by means of a Tektronix current probe amplifier.

The patterns of pacing and test stimuli delivered to the heart were programmed by using a variable interval generator and a series of Tektronix wave form and pulse generators. The output of the pulse generator triggered a Grass stimulator that delivered pulses of 2 msec duration to the ventricular stimulating electrodes. Ventricular fibrillation threshold was determined by delivering trains of rapid unipolar or bipolar pulses during the vulnerable period. The ventricle was paced by basic stimuli at a cycle length of 400 msec, and the train of rapid pulses was delivered after every 12th basic ventricular response. These pulses were 2 msec in duration and occurred at an interval of 10 msec (100/sec). The train was started 60 to 80 msec after the basic response and its duration did not extend beyond the absolute refractory period of the first premature beat evoked by the train. The intensity of the rapid stimuli was gradually increased until fibrillation resulted. The ventricular fibrillation threshold was then defined as the minimal current (expressed in milliamperes [ma]) that induced fibrillation. At the onset of fibrillation, the occluding snare on the left anterior descending artery was immediately released, and defibrillation was accomplished by direct-current countershock. A period of 15 to 20 minutes was then allowed before the next observation was made. In some experiments, the competition between pacing stimuli and normally conducted beats was achieved by pacing the right ventricle at a cycle length of 640 msec and the right atrium at 400 msec.

Results

Ventricular Fibrillation Threshold

Ventricular fibrillation threshold was determined using trains of bipolar, unipolar anodal or unipolar cathodal pulses in 13 dogs during acute coronary occlusion. The left anterior descending artery was occluded about 5 minutes before each threshold determination. Figure 1 illustrates the results obtained from one of these experiments. In panel A, the ventricular fibrillation threshold determined using bipolar stimuli was 13 ma, and fibrillation was initiated by the first premature beat coupled to the basic response at an interval of 182 msec. In panel B, the threshold with unipolar anodal stimulation was 15 ma with a coupling interval of 188 msec, and in C the threshold obtained with unipolar cathodal stimulation was 28 ma with a coupling interval of 198 msec. The results clearly indicate that ventricular fibrillation threshold with bipolar and unipolar anodal stimulation is lower than the threshold obtained by unipolar cathodal stimulation, and the first premature beat can be induced earlier by bipolar or unipolar anodal than by unipolar cathodal stimulation.

Figure 2 shows the mean values for ventricular fibrillation threshold obtained using the three differ-

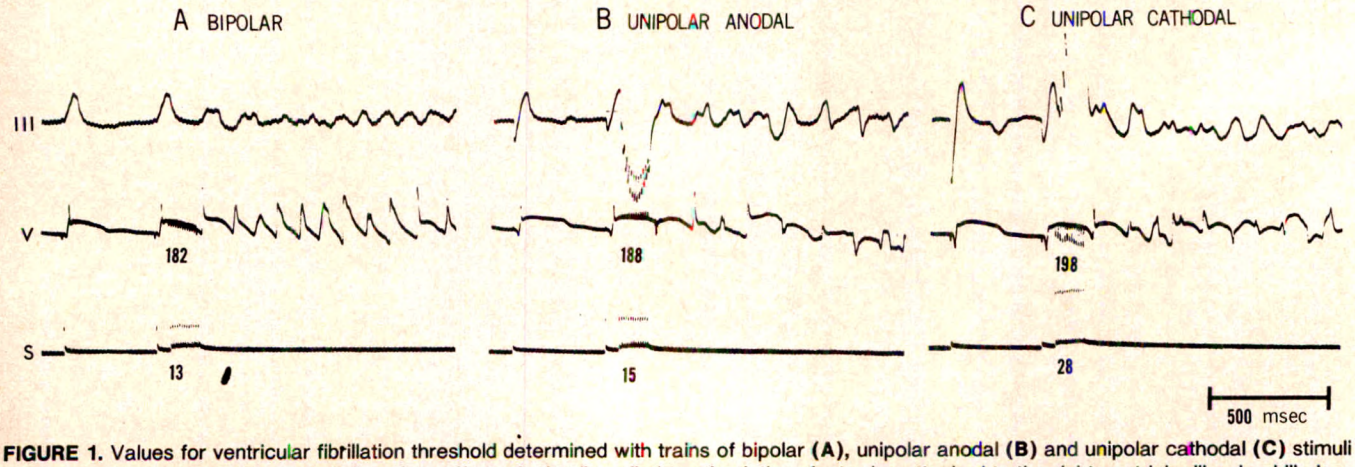

FIGURE 1. Values for ventricular fibrillation threshold determined with trains of bipolar **(A)**, unipolar anodal **(B)** and unipolar cathodal **(C)** stimuli applied during the vulnerable period. S = the artifact of stimuli applied to stimulating electrodes attached to the right ventricle; III = lead III electrocardiogram; V = local electrogram recorded at a site close to stimulating electrodes. Upper numerical values indicate coupling interval of the first premature beat in milliseconds, lower values indicate ventricular fibrillation threshold in milliamperes.

ent types of stimuli in all 13 experiments. The mean fibrillation threshold was 13.0 ± 1.6 (standard error) ma for bipolar, 13.9 ± 1.8 ma for unipolar anodal and 21.0 ± 1.9 ma for unipolar cathodal stimulation. Ventricular fibrillation threshold with both bipolar and unipolar anodal stimulation was significantly lower ($P < 0.01$) than that obtained with unipolar cathodal stimulation. The difference between fibrillation thresholds obtained with bipolar and unipolar anodal pacing was not statistically significant. In 8 of the 13 experiments, the coupling intervals of the first premature beat induced by the rapid stimuli were measured. The mean coupling interval was 187.5 ± 3.4 msec for bipolar, 191.9 ± 4.5 msec for unipolar anodal and 202.5 ± 3.8 msec for unipolar cathodal stimulation. The coupling intervals for both bipolar and unipolar anodal stimulation were significantly shorter ($P < 0.05$) than that for unipolar cathodal stimulation.

Competitive Ventricular Pacing

The effect of competition between unipolar or bipolar pacing stimuli and normally conducted beats was studied during acute myocardial ischemia in 16 dogs. Since unipolar anodal stimulation is not used in the clinical setting, only unipolar cathodal and bipolar stimuli were used to simulate the competitive pacing occurring in clinical situations. The competition was achieved by pacing the right atrium at a cycle length of 400 msec and the right ventricle at 640 msec, so that some ventricular stimuli would fall in the vulnerable period. The ventricular pacing stimuli were of 2 msec duration and delivered at an intensity of 6 ma. While the ventricle was in competitive rhythm, the left anterior descending artery was occluded. If ventricular fibrillation occurred, the occluding snare was released immediately and defibrillation was accomplished by direct-current countershock. If fibrillation did not occur, the snare was released 5 minutes after the start of occlusion. Repeat occlusion began 15 to 20 minutes after defibrillation or cessation of coronary occlusion.

The results of a representative experiment are shown in Figure 3. In panel A, during bipolar stimulation of the ventricle, ventricular fibrillation developed 2 minutes, 30 seconds after the start of coronary occlusion when an early premature beat was induced by one of the bipolar stimuli. In panel B, during unipolar cathodal stimulation, fibrillation did not develop within the 5 minute period of coronary occlusion, although early premature beats were induced by cathodal stimuli. Similar results were consistently observed on repeat trials of coronary occlusion in the 16 dogs, and the cumulative data are shown in Figure 4. Ventricular fibrillation occurred within 5 minutes after the start of coronary occlusion in 12 of 33 trials (36 percent) during competitive pacing with bipolar stimuli, and in 5 of 33 trials (15 percent) with unipolar cathodal stimuli. This difference in frequency of ventricular fibrillation was statistically significant ($P < 0.05$).

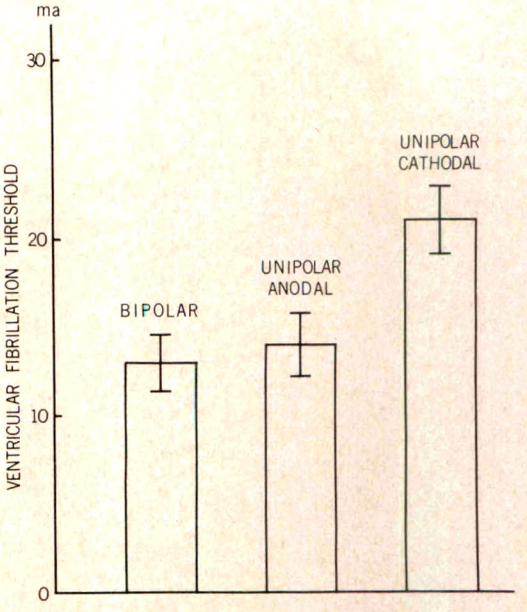

FIGURE 2. Comparison of ventricular fibrillation thresholds obtained with bipolar, unipolar anodal and unipolar cathodal stimulation in 13 dogs. The values are expressed as mean ± standard error.

Discussion

Myocardial ischemia, ventricular fibrillation and unipolar vs. bipolar stimulation: Our results clearly demonstrate that ventricular fibrillation threshold is lower and the ventricle more vulnerable

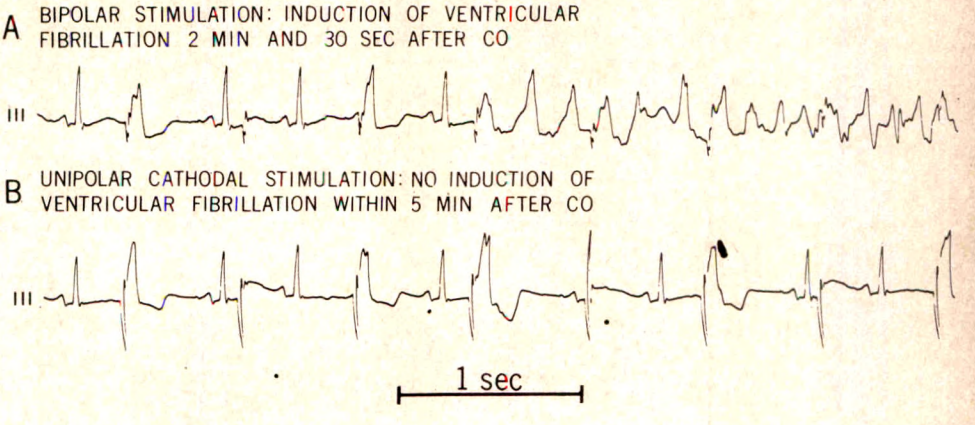

FIGURE 3. Ventricular arrhythmias resulting from competitive bipolar **(A)** and unipolar cathodal **(B)** pacing during acute coronary occlusion (CO). The artifacts of ventricular stimuli occurring at a cycle length of 640 msec are smaller with bipolar stimulation in **A.** III = lead III electrocardiogram.

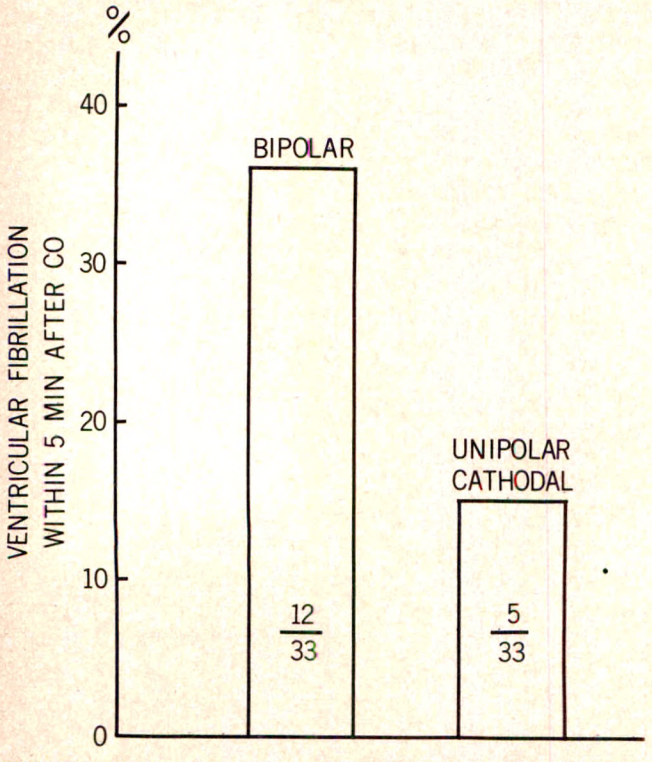

FIGURE 4. The incidence of ventricular fibrillation induced by competitive bipolar and unipolar cathodal pacing during acute coronary occlusion (CO). The data are from 33 paired trials of competitive pacing in 16 dogs.

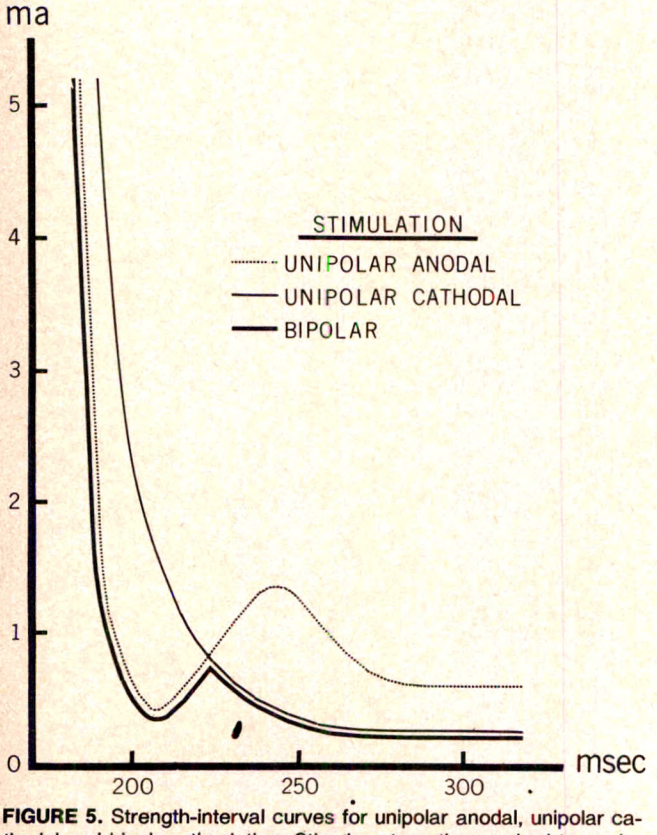

FIGURE 5. Strength-interval curves for unipolar anodal, unipolar cathodal and bipolar stimulation. Stimulus strengths required to evoke excitation are plotted on the ordinate in milliamperes and various intervals after the preceding excitation on the abscissa in milliseconds.

to fibrillation when the anodal electrode is involved unipolarly or bipolarly in ventricular stimulation during acute myocardial ischemia. They also showed that ventricular fibrillation is induced more frequently by bipolar stimuli than by unipolar cathodal stimuli during the competition between pacing stimuli and conducted ventricular beats. Our data further support the view that the risk of life-threatening ventricular arrhythmias is greater with bipolar than with unipolar cathodal pacing in the presence of acute myocardial infarction.[10] These observations are not surprising when the results of earlier experimental studies[11–13] are taken into consideration. Moe et al.[12,13] demonstrated that ventricular fibrillation occurred much more frequently with anodal stimuli than with cathodal stimuli applied to the vulnerable period. They also found that fibrillation originated from the anodal site when a bipolar stimulus was applied to the vulnerable period.

In our study, the coupling interval between the basic response and the first premature beat induced by the train of rapid stimuli was significantly shortened when the anodal electrode was involved unipolarly or bipolarly. This is also an expected finding in light of the results of earlier studies by Hoffman[14] and Cranefield[15] and their associates, who studied the strength-interval curves obtained with bipolar, unipolar anodal and unipolar cathodal stimulation. They found (Fig. 5) that during diastole the threshold for excitation is higher with anodal stimulation than with cathodal stimulation, but during the dip in the relative refractory period the reverse is true. The vulnerable period coincides with the dip, and the ventricle is most prone to fibrillation during this period. The strength-interval curve obtained with bipolar stimulation would then be a composite of the lowest portions of the anodal and cathodal curves. Thus, during the vulnerable period excitation should originate from the anodal electrode, but during diastole the cathode should be more effective in initiating excitation. These observations suggest that the shortened coupling intervals and lower ventricular fibrillation thresholds with unipolar anodal and bipolar stimulation may be due to the lower anodal threshold for excitation during the vulnerable period.

Ventricular premature beats and ventricular fibrillation: Ventricular premature beats, whether generated spontaneously or induced by pacemaker stimuli, have the potential to initiate ventricular tachycardia and fibrillation. The risk of ventricular fibrillation is particularly great when the premature beats are closely coupled to the previous beat and fall in the vulnerable period.[7,8] The ventricle is vulnerable during this period because excitability and conductivity are irregularly depressed as a result of nonuniform recovery of excitability in different segments of the myocardium. The premature impulse may travel rapidly through relatively more excitable tissues, propagate slowly through poorly excitable areas and fail to excite those still refractory. These conditions may further increase the nonuniformity of excitability and conductivity, leading to the develop-

ment of reentrant circuits and fractionation of the excitation wave front into many irregular wavelets, that is, fibrillation. The ventricle with an ischemic area should be more vulnerable to fibrillation, since reentrant activity and disorganization of the wave front are more likely to occur because of marked depression of excitability and conductivity in the ischemic area.[7,8] Our study showed that ventricular premature beats can be induced significantly earlier with unipolar anodal and bipolar stimulation than with cathodal stimulation. This earlier onset may have facilitated the induction of ventricular fibrillation since the chance of reentrant activity and subsequent disorganization of the excitation wave front is expected to be enhanced with an increase in the prematurity of ventricular excitation.[7,8]

Clinical implications: There are several possible reasons why, even with bipolar pacing, ventricular fibrillation occurs rather infrequently in clinical situations. When bipolar electrodes are inserted in the right ventricle the distal electrode may be in better contact with the endocardium than is the proximal electrode. Since the distal electrode is routinely connected to the cathode of a pulse generator, bipolar pacing may be more like unipolar cathodal stimulation in many cases. Cases in which the proximal electrode is in good contact with the endocardium, and hence true bipolar stimulation is possible, may be fewer than one might anticipate. Demand or standby pacemakers are now generally used for temporary ventricular pacing, and the possibility of pacemaker competition has been reduced significantly.[2] However, it is possible that these pacemakers may still function in the fixed-rate mode and that competitive pacing may result when the ventricular potentials registered by the bipolar electrodes are too small to be sensed by the demand pacemaker.[9] The failure of such a sensing function is less likely to occur with unipolar cathodal pacing because the amplitude of ventricular potentials recorded by the unipolar electrode is much greater.[9] In most cases of competitive bipolar pacing the intensity of bipolar stimuli falling in the vulnerable period may not be strong enough to induce ventricular fibrillation, but fibrillation will occur when the threshold is abnormally lowered during acute myocardial infarction.[7,8]

Our results indicate that unipolar cathodal pacing is potentially safer than bipolar pacing when ventricular vulnerability to fibrillation is increased, and they suggest that the incidence of pacemaker-induced ventricular fibrillation can be further reduced by the use of unipolar cathodal stimulation for temporary ventricular pacing during acute myocardial infarction. Virtually all temporary ventricular pacing is currently performed using bipolar electrodes and bipolar pulse generators. Such pacemaker systems can be easily unipolarized by connecting the distal electrode to the cathode and a remote indifferent electrode to the anode of pulse generators.

Acknowledgment

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Double Outlet Right Ventricle {S,D,L} with Subaortic Ventricular Septal Defect and Pulmonary Stenosis

Report of Six Cases

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The clinical, hemodynamic, angiocardiographic and pathologic findings are presented in an infrequent but surgically correctable type of double outlet right ventricle. This study is based on six cases, one with autopsy confirmation. In all, the viscera and atria were in situs solitus (S). A ventricular *d*-loop was present (D). There was *l*-malposition of the great arteries, the aorta being to the left of, and anterior to, the pulmonary artery (L). Hence, this anomaly may conveniently be represented as double outlet right ventricle {S,D,L}. The ventricular septal defect was subaortic because the aorta was anterior and leftward, adjacent to the ventricular septum. A bilateral conus was present beneath both the aortic and pulmonary valves, preventing any semilunar-atrioventricular fibrous continuity. The subpulmonary conus was poorly expanded, resulting in pulmonary infundibular and valvular (annular) stenosis.

The clinical features were those of cyanosis, clubbing and accentuation of the second heart sound in the pulmonary area (related to aortic valve closure). There was a systolic ejection murmur along the upper left sternal border, related to pulmonary outflow tract stenosis. Selective right and left ventricular angiocardiography was diagnostic.

Relatively early surgical correction is suggested to minimize the progression of pulmonary infundibular stenosis and to avoid acquired atresia. In this malformation, pulmonary outflow tract reconstruction is more difficult than in tetralogy of Fallot because of the rather posterior location of the pulmonary outflow tract, and because the right coronary artery crosses the stenotic pulmonary outflow tract in front of the pulmonary valve.

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This paper presents six cases of an infrequent and consequently not well known type of double outlet right ventricle that is surgically correctable.

Material and Methods

The subjects were 3 male and 3 female children whose ages ranged from 5 months to 8 years (Table I). One patient (Case 1) was examined at autopsy. The other five are alive and have been studied by cardiac catheterization and angiocardiography. Case 1 was previously presented in part by Paul et al. (their Fig. 6)[1] and by Van Praagh (his Fig. 33).[2] Case 2 was previously presented in part by Van Praagh (his Fig. 32).[2]

Results

Pathologic Anatomy

Case 1 illustrates the anatomic features of this anomaly (Fig. 1). The viscera and atria were in situs solitus (Fig. 1a and 2). A ventricular *d*-loop was present, the morphologically right ventricle being right-sided (Fig. 1, a to c, and 2) and the morphologically left ventricle being left-sided (Fig. 1, a and d, and 2). Double outlet right ventri-

cle was present, both great arteries originating entirely above the morphologically right ventricle (Fig. 1, b and c, and 2). *L*-malposition of the great arteries was present, the malposed aortic valve lying to the left (*levo*, or *l*-) and slightly anteriorly relative to the malposed pulmonary valve (Fig. 1a and 2). Because of the anterior and relatively left-sided location of the aortic valve, the ventricular septal defect was subaortic (Fig. 1b and 2), not subpulmonary (Fig. 1c and 2). The ventricular septal defect was the only outlet for the left ventricle (Fig. 1d), and the oxygenated pulmonary venous blood was directed preferentially into the aorta (Fig. 2, arrow). A bilateral conus was present, conal musculature being both subaortic (Fig. 1b) and subpulmonary (Fig. 1c). The conal musculature prevented semilunar-atrioventricular fibrous continuity (Fig. 1, b and c). All six cases had pulmonary outflow tract stenosis of various degrees of severity, due to both pulmonary infundibular stenosis (Fig. 1c) and pulmonary valvular stenosis, the pulmonary valve in Case 1 being bicuspid (Fig. 2). Briefly, therefore, the anomaly under consideration is double outlet right ventricle {S,D,L} with subaortic ventricular septal defect, bilateral conus and pulmonary stenosis.

Left-sided juxtaposition of the atrial appendages occurred in two of these six patients (Cases 4 and 6).

Clinical Findings

Cyanosis occurred at some time in all patients (Table II), but it was frequently delayed, as in tetralogy of Fallot. The age at onset of cyanosis and its severity appeared to correlate with the severity of the pulmonary outflow tract stenosis, as in tetralogy: In Case 1, cyanosis was only intermittent, apparently because the stenosis of the pulmonary outflow tract was mild (Fig. 1c); in Case 2, generalized cyanosis did not appear until age 2 years; in Case 3, cyanosis was present from birth; in Case 4, although intermittent perioral and acrocyanosis was observed with feeding during the first few days of life, constant generalized cyanosis was not present until age 3 years; in Case 5, intermittent cyanosis with crying was observed in the first 2 weeks and moderate generalized cyanosis was present by 20 months; in Case 6 the patient was thought to be acyanotic until age 10 months, when cyanosis was observed to be slight at rest, but marked with crying.

The second heart sound was accentuated in all (Table II) and was maximal in the pulmonary area. This appeared to be due to the abnormally anterior and leftward location of the aortic valve (*l*-malposition).

A systolic ejection murmur along the left sternal border was heard in all and was associated with a thrill in four of the six patients (Table II). The murmur and thrill appeared to originate from the stenotic pulmonary outflow tract.

Chest roentgenograms revealed a normal heart size in most (five of six cases, Table II). The majority had reduced pulmonary vascularity (five of six cases,

TABLE I

Locale, Sex and Age of Patients

Case no.	Center	Sex	Age
1	Toronto	M	5 mo
2	Mexico	M	8 yr
3	New Orleans	F	6 yr
4	Halifax	F	5 yr
5	San Diego	F	5 yr
6	Boston	M	19 mo

TABLE II

Salient Clinical Findings

	Case no.					
	1	2	3	4	5	6
Physical examination						
Dyspnea	+	+	+	0	0	+
Cyanosis	+	+	+	+	+	+
Accentuated S_2	+	+	+	+	+	+
Thrill, LSB	+	0	+	+	0	+
SM, LSB	+	+	+	+	+	+
Chest roentgenogram						
Cardiomegaly	+	0	0	0	0	0
Pulmonary vascularity	↑	↓	↓	↓	↓	↓
Electrocardiogram						
RAD	+	+	...	...	+	...
LAD	...	...	+	+	...	+
RVH	+	+	+	+	+	...
LVH	...	...	+	...	+	+

↑ = increased; ↓ = decreased; + = present; 0 = absent.
LAD = left (superior) axis deviation; LSB = left sternal border; LVH = left ventricular hypertrophy; RAD = right axis deviation; RVH = right ventricular hypertrophy; S_2 = second heart sound; SM = systolic murmur.

Table II). Two convexities of the left upper heart border in the posteroanterior chest roentgenogram (Fig. 3) were present in two patients (Cases 4 and 6), accurately suggesting left-sided juxtaposition of the atrial appendages.

Electrocardiograms did not present a homogeneous pattern (Table II, Fig. 4). Right axis deviation with clockwise inscription of the QRS loop was present in three cases, whereas the other three had left (superior) axis deviation with counterclockwise inscription of the QRS loop. None of these patients was thought to have a common atrioventricular valve. However, the possibility of a ventricular septal defect of the atrioventricular canal type, with or without an overriding tricuspid valve, was not excluded with certainty in the three patients with a counterclockwise and superior QRS loop in the frontal plane. Right ventricular hypertrophy was indicated in three and left ventricular hypertrophy in one; biventricular hypertrophy was suggested in two patients (Table II, Fig. 4).

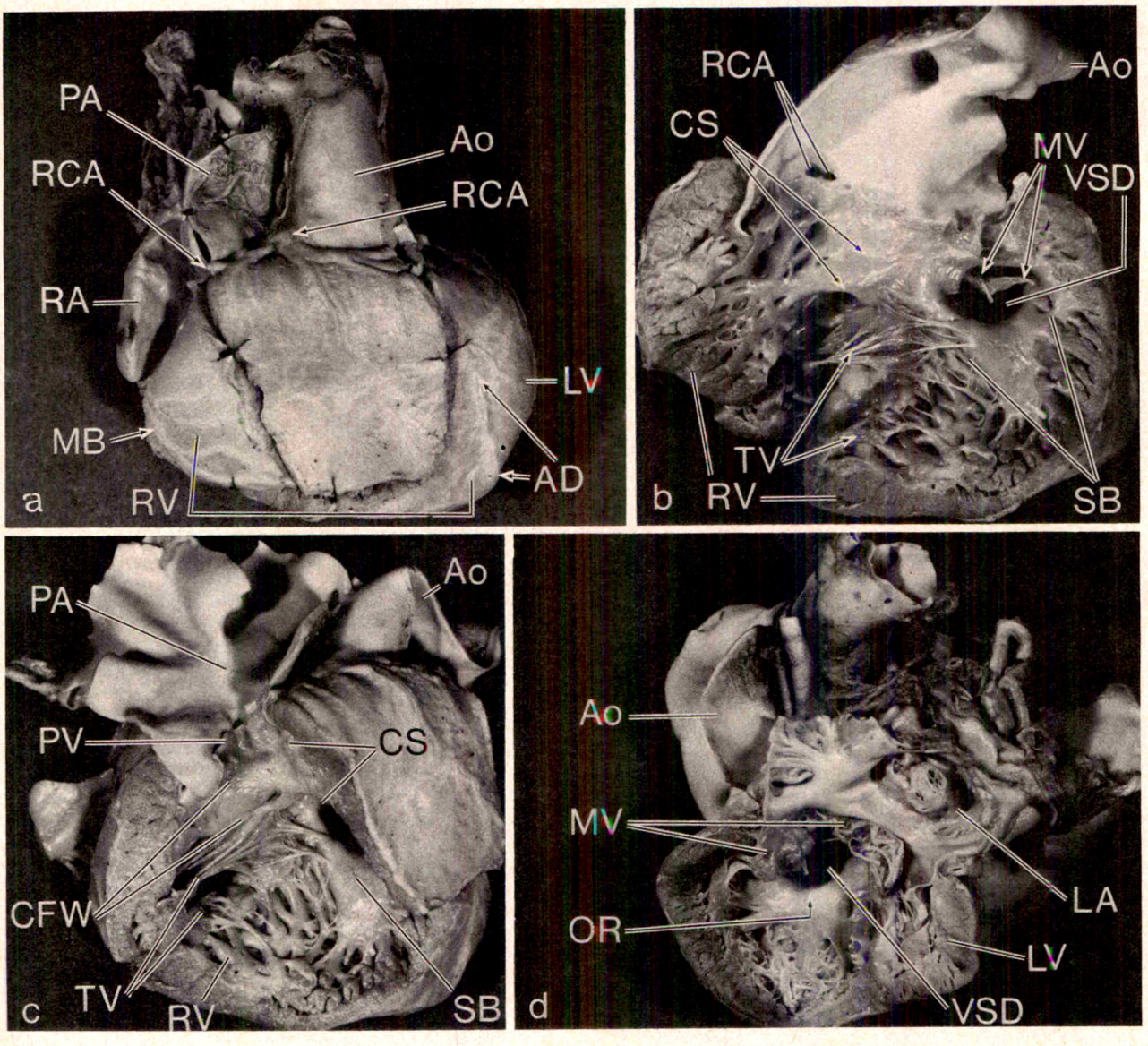

FIGURE 1. Case 1. Heart specimen. **a,** *external frontal view.* The cardiac chambers are normally interrelated, the morphologically right atrium (RA) and right ventricle (RV) being right-sided, and the morphologically left ventricle (LV) being left-sided. However, the relation between the great arteries suggests corrected *l*-transposition, the aorta (Ao) arising anteriorly and to the left of the pulmonary artery (PA). Both great arteries originate to the right of the plane of the anterior descending coronary artery (AD), accurately suggesting the presence of double outlet right ventricle. Noninversion of the ventricles is indicated by the coronary distribution; for example, the marginal branch (MB) of the right coronary artery (RCA) indicates that the right ventricle is right-sided. The smallness of the pulmonary artery compared with the aorta accurately suggests stenosis of the pulmonary outflow tract. The right coronary artery lies immediately in front of the pulmonary artery, complicating ventriculotomy from the right ventricle into the pulmonary artery. All coronary branches arise from the right coronary artery, indicating absence of the ostium of the left coronary artery. Thus, much may be deduced by careful external inspection, which should prove helpful surgically in future cases. **b,** *opened right ventricle,* viewed through subaortic incision seen in **a,** showing aortic outflow tract. The ventricular septal defect (VSD) is subaortic. The inferior rim of the defect is formed by the septal band (SB). Mild overriding of the mitral valve (MV) through the ventricular septal defect is seen. The muscular subaortic conus is well seen, the conal septum (CS) preventing fibrous continuity between the aortic valve above and the tricuspid valve (TV) and mitral valve below. CS is also known as the parietal band or crista supraventricularis. The right coronary artery has two large ostia, there being no ostium of the left coronary artery. **c,** *opened right ventricle,* viewed through subpulmonary incision seen in **a,** showing pulmonary outflow tract. Both halves of the narrowed subpulmonary conus are visible, the right (pulmonary) side of the conal septum and the subpulmonary conal free wall (CFW). The pulmonary valve (PV) is bicuspid and the pulmonary artery and branches are dilated, reflecting the mildness of the pulmonary infundibular and valvular stenosis. The subpulmonary conal musculature prevents pulmonary-tricuspid fibrous continuity. **d,** *opened left atrium* (LA), *mitral valve and left ventricle* showing mild overriding (OR) of the mitral valve through the ventricular septal defect, also seen in **b.** The left ventricle is normal in size and thickness. There is no evidence that the mild overriding of the mitral valve significantly obstructed the ventricular septal defect.

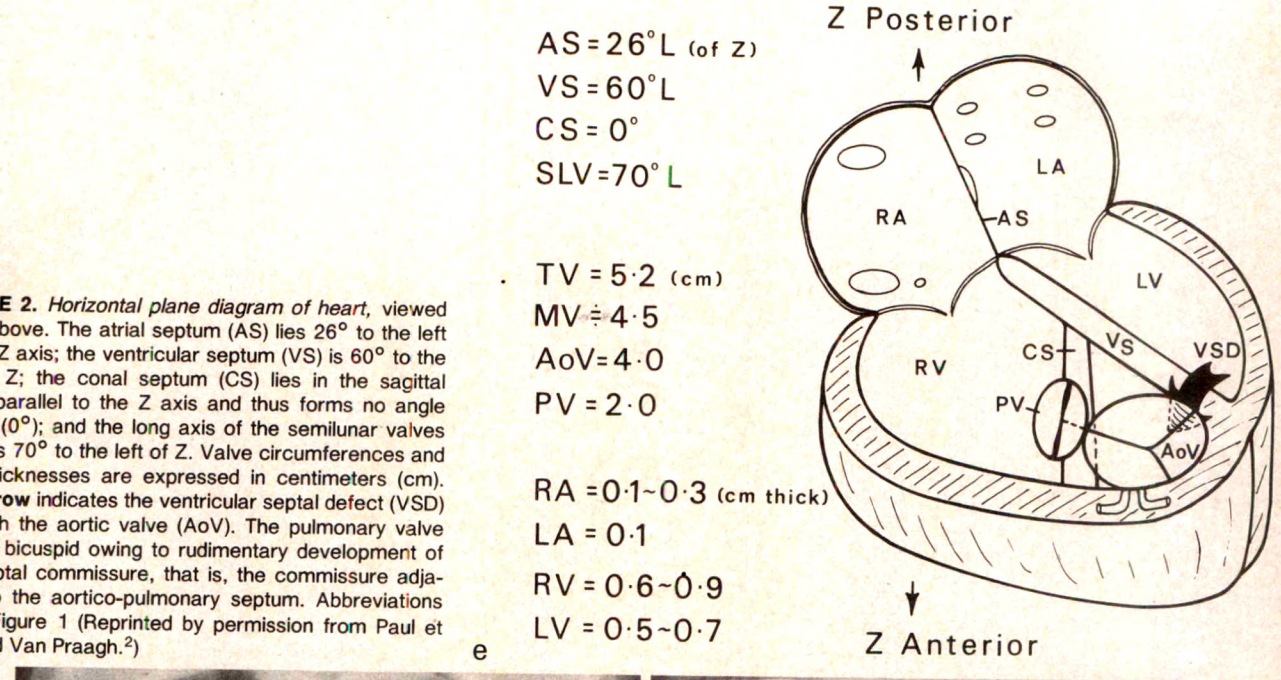

FIGURE 2. *Horizontal plane diagram of heart,* viewed from above. The atrial septum (AS) lies 26° to the left of the Z axis; the ventricular septum (VS) is 60° to the left of Z; the conal septum (CS) lies in the sagittal plane parallel to the Z axis and thus forms no angle with Z (0°); and the long axis of the semilunar valves (SLV) is 70° to the left of Z. Valve circumferences and wall thicknesses are expressed in centimeters (cm). The **arrow** indicates the ventricular septal defect (VSD) beneath the aortic valve (AoV). The pulmonary valve (PV) is bicuspid owing to rudimentary development of the septal commissure, that is, the commissure adjacent to the aortico-pulmonary septum. Abbreviations as in Figure 1 (Reprinted by permission from Paul et al.[1] and Van Praagh.[2])

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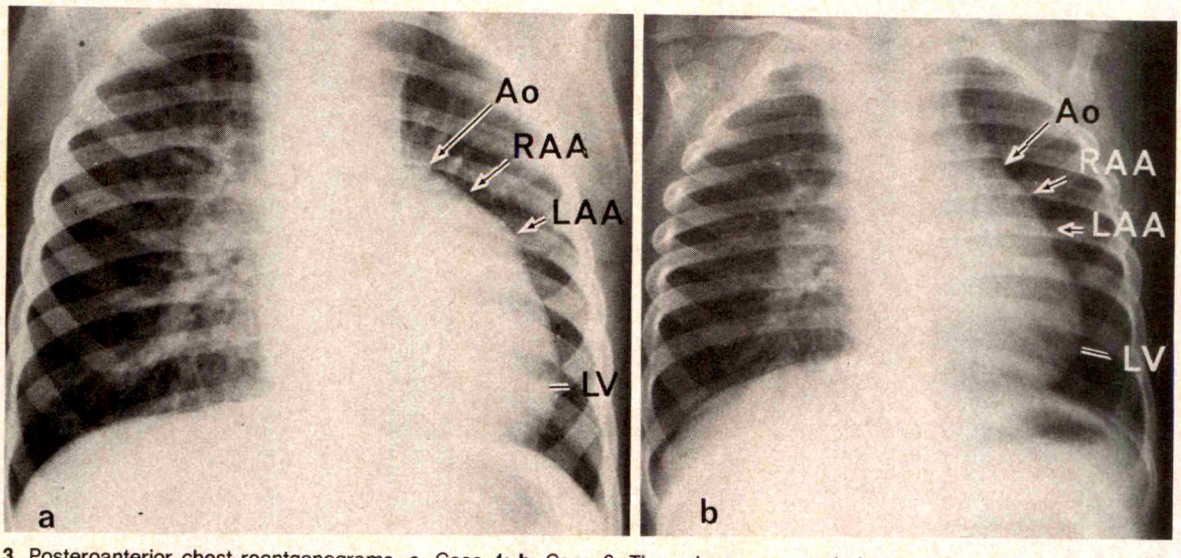


FIGURE 3. Posteroanterior chest roentgenograms. **a,** Case 4; **b,** Case 6. The pulmonary vascularity was regarded as somewhat reduced in Case 4 and mildly increased in Case 6 (Table II). In both, note the four convexities of the left heart border related to the *l*-malposed aorta (Ao), the right atrial appendage (RAA), the left atrial appendage (LAA) and the left ventricle (LV). In this entity, the left upper heart border tends to be straight or convex because of *l*-malposition of the great arteries, with or without left-sided juxtaposition of the atrial appendages.

TABLE III

Hemodynamic Findings

Sites	Case 2		Case 3		Case 4		Case 5		Case 6	
	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)
SVC	57	...	64	...	75	...	61	...	65	...
RA	56	(6)	65	(6)	71	(2.5)	58	(3)	61	(6)
RV	55	100/5	73	156/15	87	100/0	79	92/9	78	95/6
PA	66	35/20	...	...	...	...	...	...	78	22/13
Ao	66	105/62	78	132/80	92	95/60	74	92/60	90	95/54
LA	...	...	99	(6)			97	(7)	87	(6)
LV	...	110/8	85	151/12	96	110/0	85	110/16	89	98/8

Figures in parentheses indicate mean pressures.

Ao = aorta; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; Sat = saturation; SVC = superior vena cava.

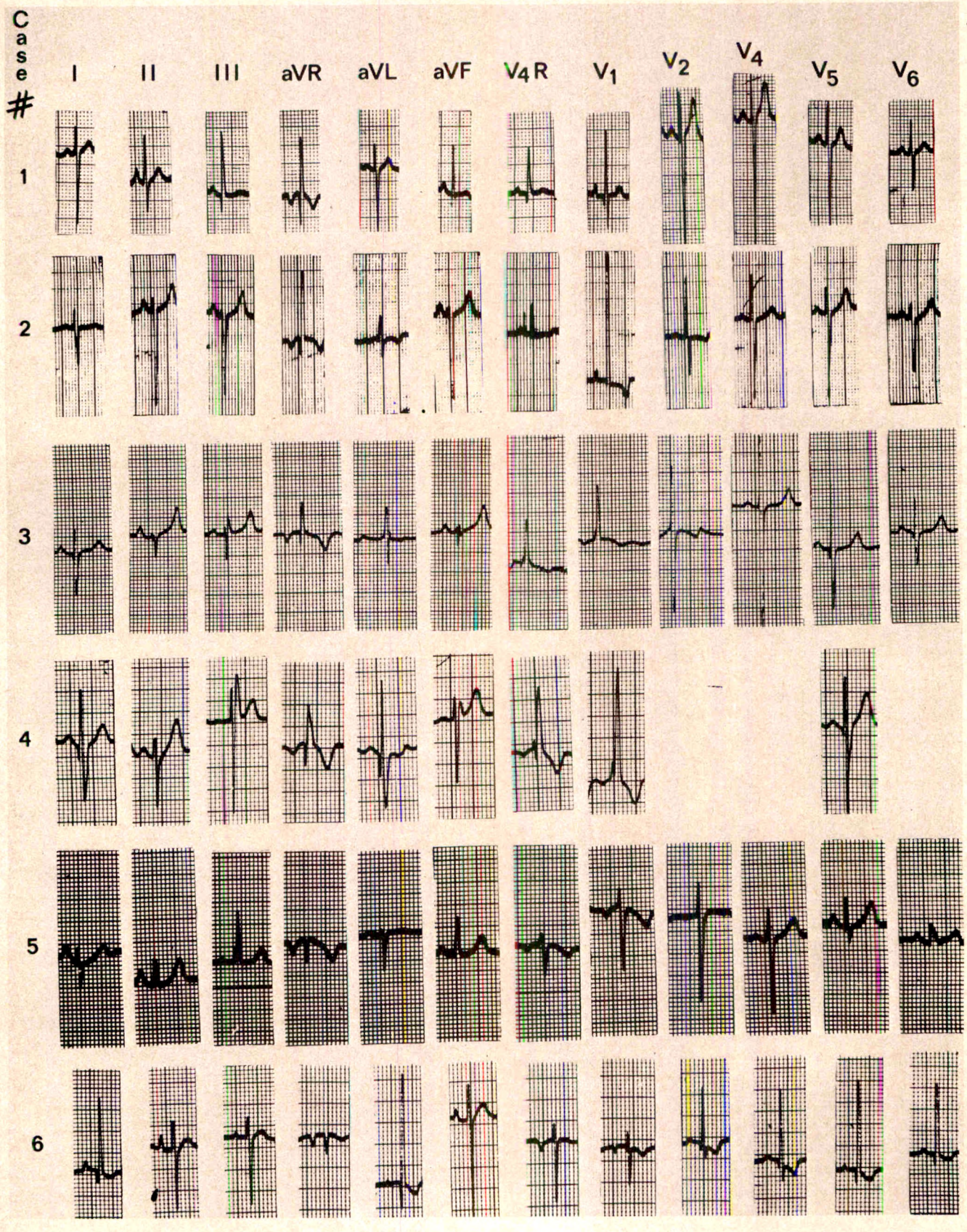


FIGURE 4. Representative electrocardiograms from all six cases. See Table II for salient interpretations. The following leads were taken at half standard: Case 2, leads V_2 and V_4; Case 5, leads V_2 and V_4; and Case 6, leads III, V_2, V_4, V_5 and V_6.

Hemodynamics and Angiocardiography

Cardiac catheterization was performed in five of these six patients (Table III). All had essentially systemic pressure in the right ventricle. All but one (Case 2) had evidence of a left to right shunt by oxygen data at the right ventricular level. The pulmonary artery was entered in only two of these five patients, and both had a sizable peak systolic gradient between the right ventricle and the main pulmonary artery, 65 mm Hg in Case 2 and 73 mm Hg in Case 6, accurately reflecting the presence of pulmonary outflow tract stenosis. However, only one of these patients (Case 6) had preferential shunting of oxygenated blood from the left ventricle into the ascending aorta by way of the subaortic ventricular septal defect, as would be anticipated from the pathologic anatomic findings (Fig. 1b and 2). In Case 6, the oxygen saturation in the ascending aorta was 90 percent, compared with 78 percent in the main pulmonary artery; but in Case 2, the oxygen saturation was 66 percent both in the ascending aorta and in the main pulmonary artery (Table III).

Angiocardiography was diagnostic (Fig. 5). Selective right ventricular injection (Fig. 5, a, b and d to m) revealed that the coarsely trabeculated morphologically right ventricle was right-sided (*d*-loop). Selective left ventricular injection (Fig. 5, c, n and o) confirmed that the relatively smoothly trabeculated morphologically left ventricle was left-sided. The presence of a ventricular *d*-loop was surprising in view of the *l*-malposition of the great arteries (abnormally located aorta to the left, levo or *l*, relative to the abnormally located pulmonary artery) (Fig. 5, a, d, f, h, i, l and n). With *l*-malposition of the great arteries, an *l*-loop resulting in ventricular inversion is usual, as in classic corrected *l*-transposition of the great arteries.

Both great arteries arose above the morphologically right ventricle. This finding was confirmed by left ventriculograms showing that the only outlet from the left ventricle was the subaortic ventricular septal defect (Fig. 5, c, n and o). After left ventricular injection, the aorta was more densely opacified than was the pulmonary artery (Fig. 5, c, n and o). This observation supports the concept of preferential flow of oxygenated blood from the left ventricle through the subaortic ventricular septal defect into the ascending aorta.

A bilateral muscular conus was present, both subaortic and subpulmonary (Fig. 5, a, f, h, i, l and n). The aortic and mitral valves were widely separated by interposed subaortic conal musculature (Fig. 5k). The conal septum (crista supraventricularis) ran approximately sagittally (Fig. 2), forming a characteristic radiolucent "teardrop" well seen in the posteroanterior projection (Fig. 5, a, d, f, h, i and l).

The pulmonary valve was to the right, posterior and slightly inferior relative to the aortic valve. Occasionally a jet was seen through the pulmonary valve (Fig. 5, a and i), accurately indicating the presence of pulmonary valvular stenosis. However, the infundibulum below the pulmonary valve also was stenotic in all cases.

Discussion

Double outlet right ventricle of the {S,D,L} type is uncommon. It was first described, to our knowledge, by Birmingham[3] in 1893. Since that time, case reports of this anomaly have been few.[1,2,4–11] Successful surgical repair was first reported in 1972 by Danielson et al.[9] and by Lincoln.[10]

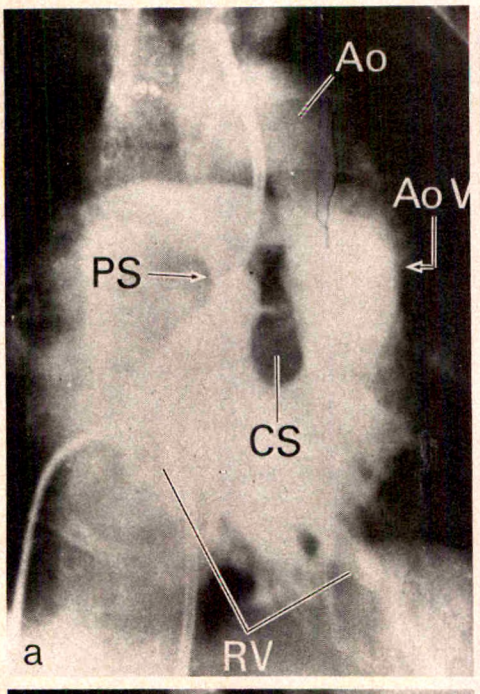
In the interests of historical perspective, our Case 1 represents more complete documentation of the fifth known case, previously reported in part by Paul et al. (their Fig. 6)[1] and by Van Praagh (his Fig. 33).[2] Our Cases 2 to 6 are, to our knowledge, the 15th to 19th reported cases, respectively, of this little known cardiac malformation.

Clinical Features

This anomaly is somewhat suggestive of tetralogy of Fallot: cyanosis, clubbing, right ventricular impulse, ejection systolic murmur along the upper left sternal border, and right ventricular hypertrophy in the electrocardiogram (Fig. 4). However, features inconsistent with tetralogy are equally striking. The second heart sound is accentuated and may be palpable in the pulmonary area. The frontal chest roentgenogram does not show a coeur en sabot contour. Although the pulmonary vascularity is usually reduced (Table II), the upper left heart border is likely to be unusually straight, or even convex, suggesting the possibilities of *l*-transposition, or left-sided juxtaposition of the atrial appendages, or both (Fig. 3). In some cases, the electrocardiogram is unlike that of typical tetralogy, and the tracing shows an atrioventricular canal type of counterclockwise and superior frontal QRS loop (Fig. 4).

If the plain chest roentgenographic appearance of the left upper heart border suggests corrected *l*-transposition (probably with pulmonary stenosis and ventricular septal defect in view of the reduced pulmonary vascularity and the systolic ejection murmur), one would then reexamine the electrocardiogram for signs of ventricular inversion.[12] Briefly, there are none (Fig. 4). Hence, careful consideration of the clinical data should suggest the possibility of *l*-malposition of the great arteries, without ventricular inversion, with pulmonary stenosis and ventricular septal defect. Thus, clinical data alone may indicate an anatomically accurate diagnosis.

What is the precise arterioventricular relation: single outlet each ventricle of the anatomically corrected[13] type, double outlet right ventricle or double outlet left ventricle? Although the aforementioned noninvasive data do not clarify this question, it seems likely that echocardiography could be helpful in this regard. In this malformation, echocardiography might suggest double outlet right ventricle by show-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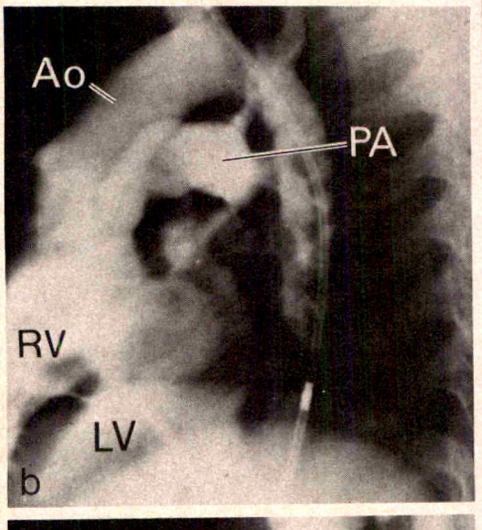
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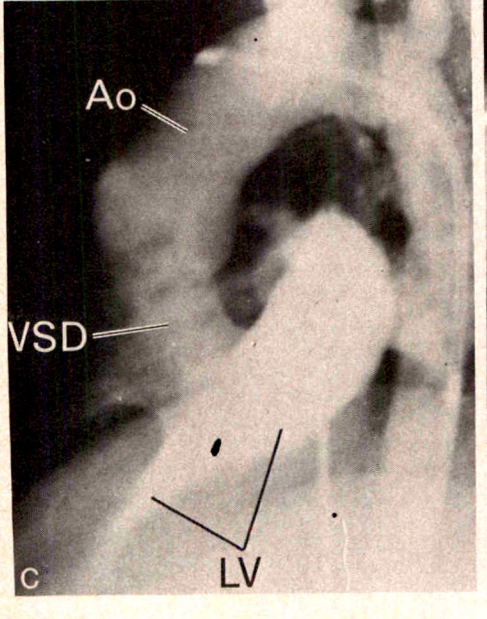
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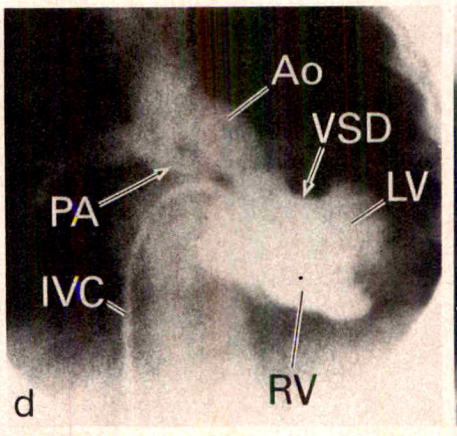
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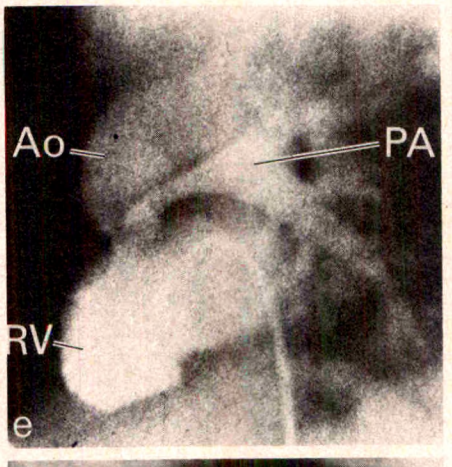
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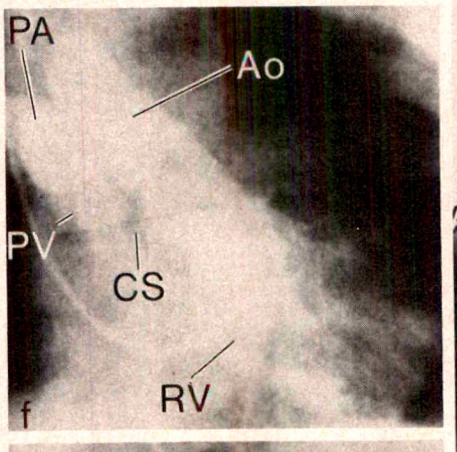
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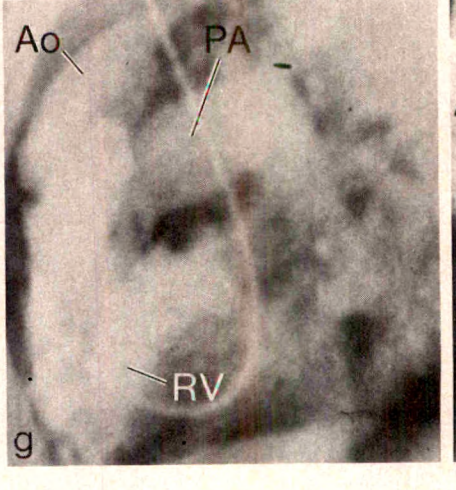
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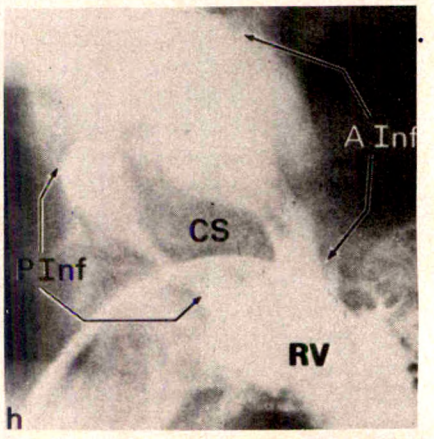
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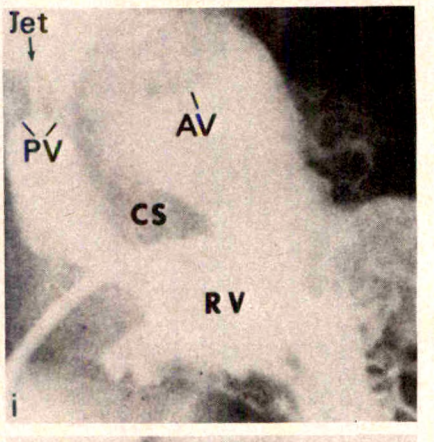
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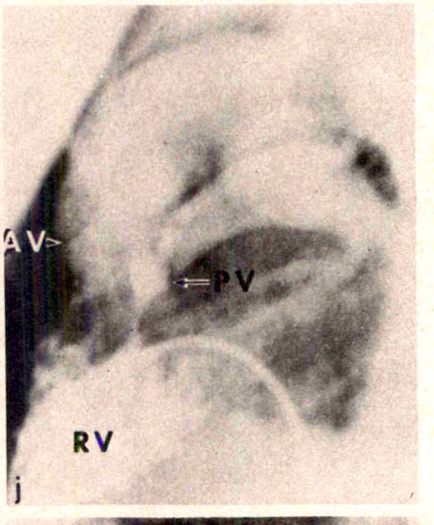
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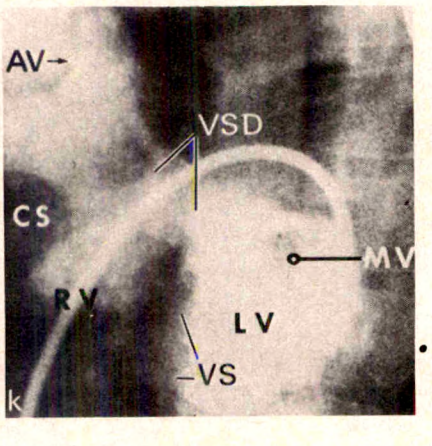
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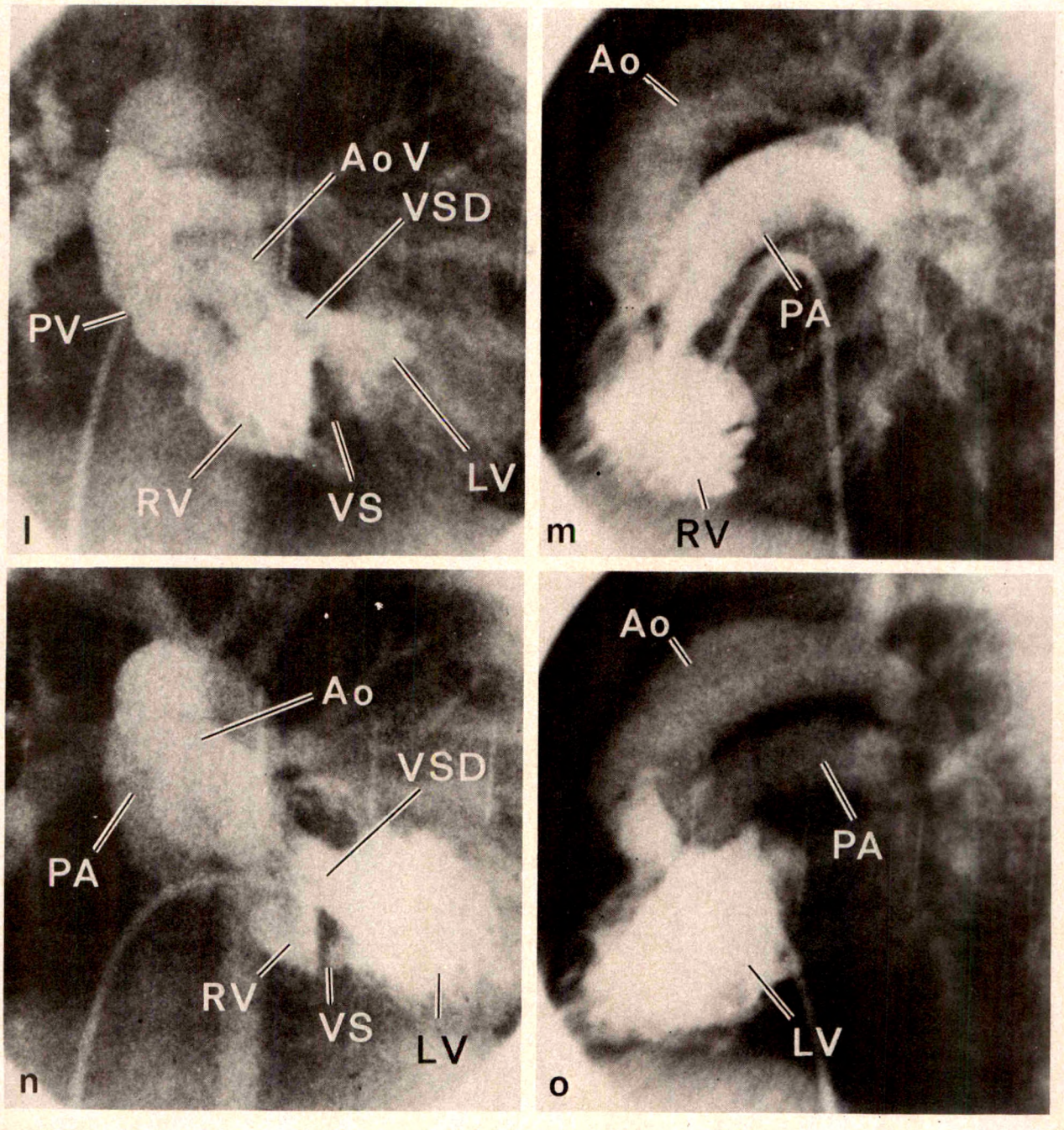

FIGURE 5. Angiocardiograms. *Case 2,* selective right ventricular injection in posteroanterior projection **(a),** in left lateral projection **(b),** and selective left ventricular injection, left lateral projection **(c).** *Case 3,* selective right ventricular injection in posteroanterior projection **(d)** and in left lateral projection **(e).** *Case 4,* selective right ventricular injection in posteroanterior projection **(f)** and in left lateral projection **(g).** *Case 5,* selective right ventricular injection in posteroanterior projection **(h** and **i),** in left lateral projection **(j)** and selective left ventricular injection by means of a catheter through the mitral valve (MV) in left anterior oblique projection **(k).** *Case 6,* selective right ventricular injection in posteroanterior projection **(l),** left lateral projection **(m)** and selective left ventricular injection in posteroanterior projection **(n)** and left lateral projection **(o).** In all, the heart is left-sided. The viscera and atria are in situs solitus, as is indicated by the normal location of the catheter in the inferior vena cava (IVC). The ventricles are not inverted (*d*-loop), as is shown by the coarse trabeculation and globular configuration of the morphologically right ventricle (RV) and by the relatively fine trabeculation and characteristic configuration of the morphologically left ventricle (LV). The presence of double outlet right ventricle is proved by selective left ventricular injection **(c, k, n,** and **o)** which shows that both the aorta (Ao) and the pulmonary artery (PA) arise above the right ventricle, the only outlet from the left ventricle being the subaortic ventricular septal defect (VSD). The wide separation between the aortic valve (AV, or AoV) and the MV is well seen in **k.** All cases have *l*-malposition of the great arteries, the aortic valve lying well to the left of the pulmonary valve (PV). The conal septum or crista supraventricularis (CS) forms a characteristic radiolucent "teardrop" in the posteroanterior projection **(a, f, h, i, l),** separating the aortic and pulmonary outflow tracts. All cases have a bilateral conus or infundibulum beneath the aortic valve (A Inf) and beneath the pulmonary valve (P Inf), and all have pulmonary outflow tract stenosis (PS). PS may be both infundibular **(h)** and valvular, with a jet **(i).** In cases with juxtaposition of the atrial appendages, the right ventricle may be somewhat small compared with the left ventricle **(l to o).** (Panels a and b reprinted by permission from Van Praagh.[2])

ing, for example, wide separation between the mitral valve and both semilunar valves. Hence, it is conceivable that this complex malformation could be diagnosed accurately by noninvasive techniques.

Diagnosis

Cardiac catheterization (Table III) and, in particular, selective biventricular angiocardiography (Fig. 5) permitted accurate diagnosis. The presence of a classic corrected transposition type of relation between the great arteries (*l*-malposition*) did not obscure the fact that the ventricles were not inverted. This feature was obvious both by selective ventriculography (Fig. 5) and by electrocardiography (Fig. 4) and could be further confirmed by coronary arteriography because the coronary distribution is characteristic for each ventricle—morphologically right and morphologically left. The presence of double outlet right ventricle, subaortic ventricular septal defect and pulmonary outflow tract stenosis also was clear (Fig. 5). However, there was some diagnostic hesitancy due to lack of familiarity with this malformation.

Some diagnostic problems have not been entirely resolved. Why do the electocardiograms of Cases 3, 4 and 6 have a counterclockwise and superior frontal QRS loop (Fig. 4)? Although these cases do not present angiocardiographic findings diagnostic of common atrioventricular valve, a ventricular septal defect of the atrioventricular canal type could be present, perhaps in association with overriding of the tricuspid valve and with some hypoplasia of the right ventricle (Fig. 5, l and n). Two of these patients (Cases 4 [Fig. 3a] and 6 [Fig. 3b]) had juxtaposition of the atrial appendages. Like asplenia, juxtaposition is a syndrome.[7] Of 42 patients with juxtaposition examined at autopsy, 71 percent had hypoplasia of the right ventricle.[7] Hence, juxtaposition should suggest the possibility of right ventricular hypoplasia, which in turn may be related to the aforementioned left (superior) axis deviation found in half of these patients (Fig. 4).

Embryology

The ventricular loop folded normally to the right (*d*-loop). The conotruncus for unknown reasons twisted to the left (*l*-malposition) instead of to the right. Both the subaortic and the subpulmonary parts of the conus persisted (bilateral conus), neither undergoing absorption.[18] Although the subpulmonary conus persisted, it remained poorly expanded, resulting in pulmonary infundibular stenosis with a small pulmonary annulus (the pulmonary annulus being the "back door" of the pulmonary infundibulum). The subaortic ventricular septal defect appears to be due to malalignment of the *l*-malposed conotruncus above, relative to the normally located ventricles and ventricular septum below (Fig. 1b). Normally, the conal septum (parietal band) largely fills the space above the septal band and ventricular septum (Fig. 6). In this malformation, however, the conal septum developed in an anteroposterior plane (Fig. 2), intersecting the ventricular septum just behind the septal band and above the tricuspid valve, resulting in a subaortic ventricular septal defect (Fig. 1b). This sagittal location of the conal septum above the right ventricle also squeezed the pulmonary outflow tract between the conal septum to the left, and the tricuspid valve and right ventricular free wall to the right (Fig. 1c). This anomaly is more than a malalignment of the conotruncal septum relative to the ventricular septum. The *entire* conotruncus—septum and free walls—is malposed relative to the ventricles and ventricular septum. The origin of this conotruncal malformation is unknown.

Surgical Problems

As Danielson et al.[9] and Lincoln[10] have shown, it is readily possible to connect the aorta with the left ventricle by way of the subaortic ventricular septal defect by utilizing a tunnel-like prosthesis to reconstruct the left ventricular outflow tract (Fig. 1b). However, the pathologic anatomy of this malformation does pose several surgical difficulties:

1. **Course of right coronary artery:** The right coronary artery runs across the stenotic pulmonary outflow tract at the level of the pulmonary valve (Fig. 1a). This course of the right coronary artery would appear to preclude a vertical incision through the pulmonary infundibulum, valve and artery, as can be made in tetralogy. (If deemed necessary and advisable, the right coronary artery could perhaps be transected and subsequently reconstituted by a venous or other jump graft.)

This surgically important course of the right coronary artery was not obvious on selective ventriculography (Fig. 5). Aortic root injection or right coronary arteriography would no doubt demonstrate the course of the right coronary artery clearly. It should perhaps be added that this is not a coronary anomaly. Indeed, the course of the right coronary artery in the right atrioventricular sulcus is normal (Fig. 1a). The abnormality is the location of the pulmonary outflow tract to the right of, and mildly posterior to, that of the aorta. This surgically inconvenient relation between the right coronary artery and the pul-

* *L*-malposition[14] is preferred to *l*-transposition because, accurately speaking, both great arteries are not transposed. Although the aorta is transposed above the right ventricle, the pulmonary artery is not transposed above the left ventricle. The term malposition is convenient for those transposition-like anomalies in which transposition is not present in the accurate, original meaning[15,16] of this term. The concept of malposition of the great arteries applies accurately in double outlet right ventricle, double outlet left ventricle, single ventricle without a ventricular septum (types B, C and D),[17] and anatomically corrected relations between the great arteries and the ventricles. The designation malposition makes it possible to use the term transposition accurately. Since malposition does not specify the relation between the great arteries and the ventricles, it is essential to state the type of arterioventricular relation, for example, double outlet right ventricle, or double outlet left ventricle, and so on. Hence, the anomaly under consideration is double outlet right ventricle with *l*-malposition of the great arteries.

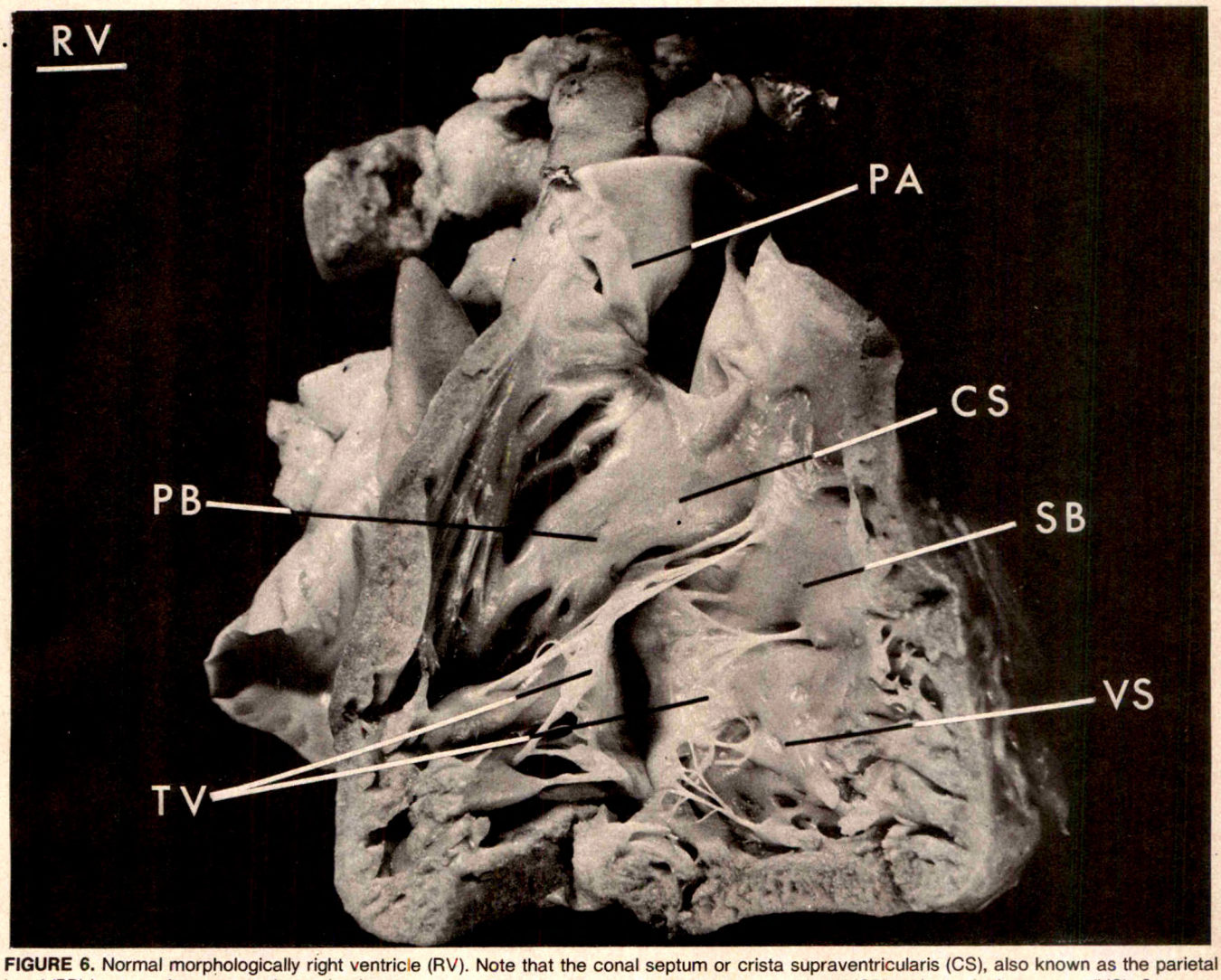

FIGURE 6. Normal morphologically right ventricle (RV). Note that the conal septum or crista supraventricularis (CS), also known as the parietal band (PB) because it runs onto the parietal or free wall, largely fills the space above the septal band (SB) and ventricular septum (VS). Compare this normal situation with Figures 1b and 2. In the latter, malposition of the conal septum leaves the space above the septal band wide open, resulting in a subaortic ventricular septal defect. PA = pulmonary artery; TV = tricuspid valve. (Reproduced from Van Praagh et al.[19])

monary outflow tract is an integral part of this malformation. It is to be expected. Consequently, right coronary arteriography could be regarded as unnecessary because it may be assumed that the course of the right coronary artery is normal, and hence that it lies directly in front of the pulmonary valve. Hence, whether or not one insists on performing right coronary arteriography preoperatively is regarded as a matter of personal preference; one could reasonably adopt either position.

2. Pulmonary outflow tract stenosis: The state of the pulmonary outflow tract in this malformation is highly variable. Occasionally there may be no pulmonary outflow tract stenosis, as in two of the four cases of Hallermann et al.[8] However, pulmonary outflow tract stenosis appears to be the rule in this malformation and it may be mild (Fig. 1c), moderate (Fig. 5, a, b, f and i), or severe (Fig. 5, d and e). When mild to moderate, the pulmonary outflow tract stenosis can be alleviated successfully by excision of subpulmonary conal musculature,[9,10] by pulmonary valvotomy[9,10] and by patching the pulmonary annulus after elevating the right coronary artery.[10]

However, when the pulmonary outflow tract stenosis is severe, as in Case 3 (Fig. 5, d and e), it appears that the pulmonary outflow tract must be bypassed. This can be accomplished early in life by a Blalock-Taussig or Waterston anastomosis, and later (when the pulmonary artery is large enough) by a Rastelli type of valved conduit between the right ventricle and the main pulmonary artery, to the right of the ascending aorta (Fig. 1a). To our knowledge, the latter procedure has not been performed.

It is expected that pulmonary outflow tract stenosis in this malformation will prove to be progressive, as in tetralogy of Fallot. Hence, relatively early surgical correction would appear to be indicated to avoid the surgical difficulties associated with the development of severe pulmonary outflow tract stenosis or acquired atresia.

3. Abnormal insertion of mitral valve: Abnormal insertion of the mitral valve into the inferior rim of the ventricular septal defect (Fig. 1b), or overriding of the mitral valve through the ventricular septal defect (Fig. 1d) could conceivably obstruct the left ventricular outflow tract—the ventricular septal defect—to a significant degree. This potential problem has not been recognized in any case to date, but the findings in Case 1 (Fig. 1, b and d) suggest that it would be well to bear this possibility in mind. If this complication occurs and if it is recognized, it may well be possible to solve this problem by excision of the obstructive mitral valve tissue, followed by mitral valve replacement.

Acknowledgment

We thank Terence Wrightson, Marilee Caliendo and Pauline McRae for photography, Donna Farina for lettering, and Eleanor Monkouski for secretarial assistance.

Addendum

After this paper was completed, Dr. John W. Kirklin performed successful correction in Case 5 (Tables I to III). On April 17, 1974, the patient was cooled to 22° C and the aorta was crossclamped for 62 minutes. Cardiopulmonary bypass was begun at 2.2 liters/min per m^2, but during aortic crossclamping was reduced to 0.5 liter/min per m^2 for 35 minutes, then 1.0 liter/min per m^2 for 5 min, and 1.6 liters/min per m^2 thereafter. Dr. Kirklin performed the procedure mentioned in the Discussion under Surgical Problems but with one important difference. He found that the valved external conduit from the right ventricle had to be placed to the *left* of the ascending aorta and connected with the left pulmonary artery (rather than to the right, as we had thought), in order to avoid compression of the conduit between the sternum and the heart. This is the first time, to our knowledge, that this anomaly has been corrected using a conduit to bypass the pulmonary outflow tract stenosis. Dr. Kirklin also closed a patent foramen ovale with two rows of continuous sutures, and he observed previously unsuspected left-sided juxtaposition of the atrial appendages. Postoperatively her skin color is pink and she is doing well. Her second heart sound, formerly single, is now split.

In addition, since completion of this paper, Dr. Fergus Shiel has shown us a seventh case of double outlet right ventricle {S,D,L} that occurred in a female infant who died at age 3 months from congestive heart failure (Medical College of Virginia Autopsy number 56/65). The cause of death is noteworthy, this being the third known case of double outlet right ventricle {S,D,L} *without* pulmonary outflow tract stenosis (the first two cases without pulmonary stenosis being those of Hallermann et al.[8]). She had dextrocardia, all previous patients with this malformation having had a left-sided heart. This patient also had left-sided juxtaposition of the atrial appendages, as did half of our patients (Cases 4 to 6). Dr. Shiel's patient also had a bilateral conus, multiple ventricular septal defects—high (subaortic) and low (large muscular),—a large secundum atrial septal defect, a small right superior vena cava and a large persistent left superior vena cava to the coronary sinus and thence to the right atrium.

Recently, one of us (P. M. W.) studied a 5 7/12 year old Filipino girl at cardiac catheterization and angiocardiography. This case proved to be an eighth example of double outlet right ventricle {S,D,L} with subaortic ventricular septal defect, moderate infundibular pulmonary stenosis, and a right aortic arch—the latter heightening the clinical resemblance to the tetralogy of Fallot.

After acceptance of this manuscript, Dr. De la Cruz and her colleagues published another autopsy-proved case of double outlet right ventricle of the {S,D,L} type with a secundum type of atrial septal defect, a ventricular septal defect, without pulmonary stenosis (de la Cruz MV, Amoedo M, Rivera F and Attie F: Arterioventricular relations and their classification. Two specimens of arterioventricular discordance and review of published reports. Br Heart J 36: 539–553, 1974). In addition, one of us (C. P-T) has recently found another example of double outlet right ventricle {S,D,L} with moderate pulmonary outflow tract stenosis in a 5 year old boy. Interestingly, the ventricular septal defect appeared angiocardiographically to be subpulmonary, rather than subaortic. Thus, this patient is the 23rd known patient with this rare form of double outlet right ventricle.[1–11]

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Echocardiography in Atrioventricular Canal Defect

A Clinical Spectrum

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Echocardiographic examinations were performed in 30 children with atrioventricular (A-V) canal defect to determine the diagnostic value of recording A-V valve motion. Although a wide spectrum of abnormal movement was observed, four main diagnostic types emerged. Type 1, prolonged mitral-septal approximation during diastole, resulted from anterior displacement of the cleft anterior mitral leaflet. Type 2, the most diagnostic motion, was recorded when the common anterior A-V leaflet traversed the interventricular septum. Type 3 motion reflected posterior displacement of the septal tricuspid leaflet, which appeared to arise from the interventricular septum. Normal posterior diastolic motion of the septal leaflet was never recorded. Type 4, double contour of the mitral valve during systole and marked duplication of the systolic image, corresponded to irregularities in the mitral valve. When these patterns are recorded in a patient with congenital heart disease the diagnosis of A-V canal defect can be made with confidence.

Proper management of infants and children with a complete atrioventricular (A-V) canal defect requires early diagnosis and differentiation from patients with a large ventricular septal or ostium primum atrial septal defect. Although no particular irregular mitral valve motion has been recorded by ultrasonic techniques in patients with a ventricular septal defect, abnormal motion of the anterior mitral leaflet, ascribed to cleft formation, has been associated with the ostium primum defect.[1] Since one of the main anatomic features of the canal lesion is cleft formation of the A-V valves,[2–5] in this study we attempted to delineate A-V valve motion ultrasonically with the hope of establishing a means of diagnosis.

Materials and Methods

Thirty children, ranging in age from 1 week to 13 years and previously proved to have an A-V canal defect by cardiac catheterization and angiocardiography, were recalled for echocardiographic study. Seventeen were female and 13 male. Twenty patients had the typical clincal features of Down's syndrome. Further anatomic documentation was made in three patients at operation and in five at postmortem examination. An additional 20 patients, 10 with an ostium primum atrial septal defect and 10 with a large ventricular septal defect, were studied to compare their echocardiographic findings with those in patients with a proved A-V canal defect.

The examinations were performed using a Smith-Kline Ekoline 20A echocardiographic machine with a 2.25 megahertz, 5 cm focused transducer. Early studies utilized Polaroid® reproductions; a Honeywell 1856 strip chart recorder was used for later examinations. The echocardiographic study included a scan from the apex of the heart to the aorta, as well as identification of the tricuspid valve in every case.[6] In addition to routine analysis of the echocardiogram, special attention was focused upon the position and motion of the mitral and tricuspid valves.

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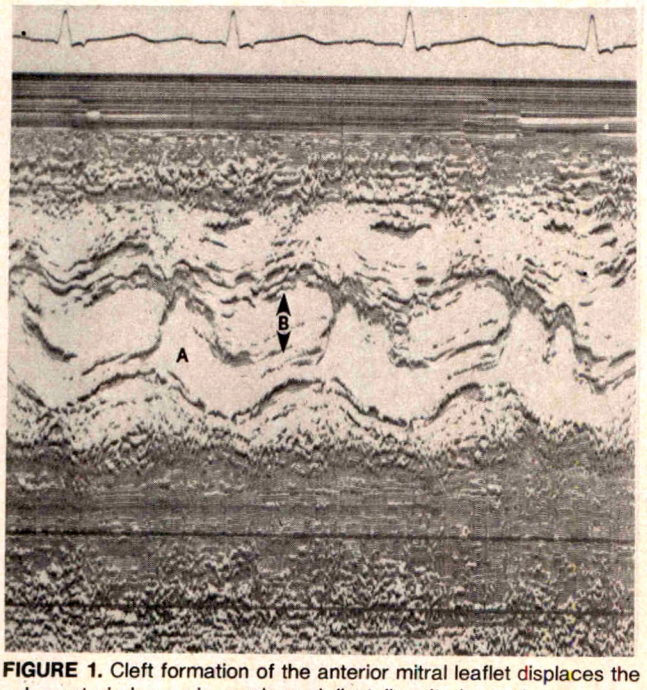

FIGURE 1. Cleft formation of the anterior mitral leaflet displaces the valve anteriorly causing prolonged diastolic mitral-septal approximation (A) and narrowing of the septal-mitral distance during systole (B) in this patient with an ostium primum defect.

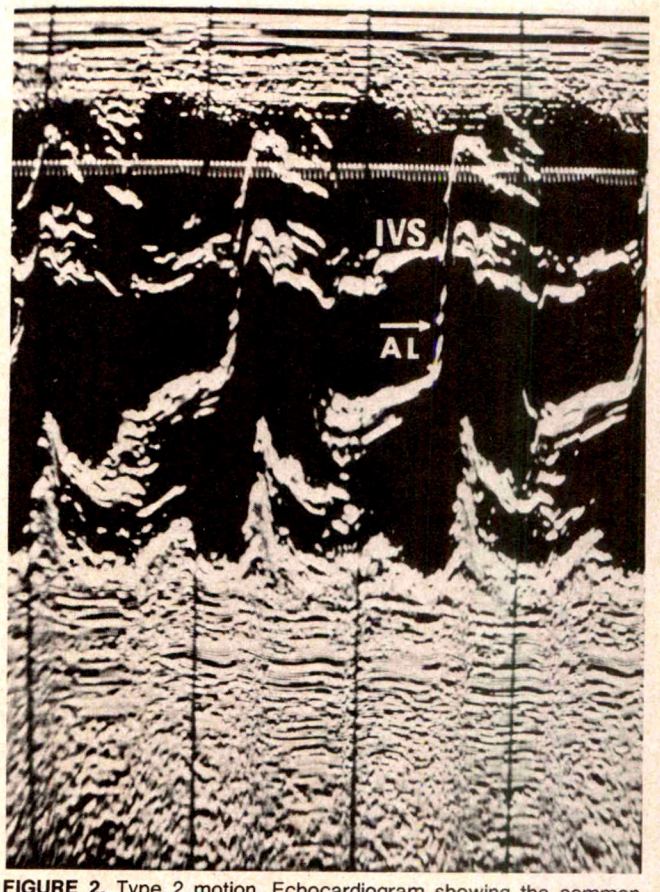

FIGURE 2. Type 2 motion. Echocardiogram showing the common anterior leaflet (AL) traversing the interventricular septum (IVS).

Results

Four main types of A-V valve motion were noted in the patients with a complete canal defect:

1. *Anterior displacement of the typical M-shaped mitral valve motion,* so that the E to F slope fused with the interventricular septum, was noted in 26 (87 percent) of patients with an A-V canal defect, 9 (90 percent) of those with an ostium primum defect and in none of those with a large ventricular septal defect (Fig. 1).

2. *The common anterior A-V leaflet was observed to traverse the interventricular septum* in 20 (67 percent) of the patients with a complete A-V canal defect (Fig. 2). This abnormality of valve motion was not noted in patients with either an ostium primum or ventricular septal defect.

3. *Various types of tricuspid valve motion* were registered. It was relatively easy to record simultaneously the mitral and tricuspid valve echoes in most

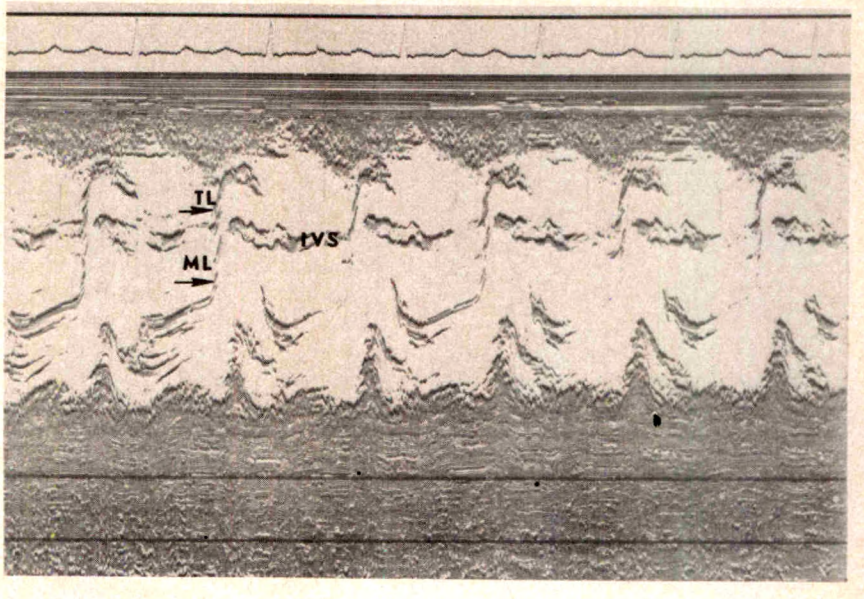

FIGURE 3. Type 3 motion. This motion can be observed upon careful examination of the opening diastolic slopes of the mitral (ML) and tricuspid (TL) leaflets. The tricuspid leaflet appears to arise from the interventricular septum (IVS), often capping the mitral valve and assuming the pattern of type 2 motion.

patients with an A-V canal defect. This was also possible in patients with a large ventricular septal defect, but not in those with an ostium primum defect. On the other hand, tricuspid valve motion in patients with a canal defect often was recorded displaced posteriorly toward the interventricular septum so that it appeared to be a continuation of mitral valve motion, a finding that simulated type 2 motion (Fig. 3). Normal septal leaflet motion, which moves the tricuspid valve posteriorly during diastole, could not be recorded in any patient with an A-V canal defect.

4. *Double contour of the mitral leaflet during diastole* was observed in only 12 (40 percent) of the patients with a canal defect (Fig. 4) and in no patient with the other two defects. Eighty-three percent of the patients with an A-V canal defect had marked duplication of the systolic image of the mitral valve. This finding was usually observed throughout the entire left ventricular scan.

Discussion

Although a wide spectrum A-V valve motion was demonstrated in the patients with an A-V canal defect, four main types emerged from this study.

Type 1. Anterior displacement of anterior mitral leaflet: The first type corresponded to the abnormal motion of the anterior mitral leaflet reported by Gramiak and Nanda[1] in patients with an ostium primum atrial septal defect. Anterior displacement of the anterior mitral leaflet resulting from cleft formation causes prolonged approximation of the leaflet to the interventricular septum during diastole and narrowing of the left ventricular outflow tract during systole. Since a more severe form of clefting occurs with a complete A-V canal defect, it was not surprising to identify prolonged mitral-septal approximation in 87 percent of these patients (Fig. 1). While prolonged approximation was documented in nine (90 percent) of our patients with an ostium primum defect, it did not occur in any patient with a ventricular septal defect even though the mitral excursion often touched the interventricular septum in the latter group of patients.

Although no standard echocardiographic measurements are available for the normal left ventricular outflow tract in children of different ages and sizes, the outflow tract definitely appeared narrowed in most of our patients with A-V canal and ostium primum lesions. When prolonged mitral-septal approximation, narrowing of the left ventricular outflow tract and paradoxical motion of the interventricular septum (the latter finding associated with the ostium primum defect)[7] are considered together, the three defects can be differentiated (Table I).

Type 2. A common anterior A-V leaflet traversing the interventricular septum: This remarkable type of abnormal motion was recorded only in children with an A-V canal defect (Fig. 2). It is necessary to visualize the anatomy of the common anterior A-V leaflet and its relation to the interventricular septum to appreciate this peculiar pattern. Clefting in the anterior mitral and septal tricuspid leaflets is responsible for the formation of two common A-V leaflets: the common anterior and posterior leaflets (Fig. 5). Since the common anterior leaflet moves diagonally to the interventricular septum,[8] parts of that leaflet can be recorded ultrasonically within the left ventricle during systole and then move to a position within the right ventricle during diastole.

There are two anatomic reasons why this diagnostic pattern was recorded in only 67 percent of the

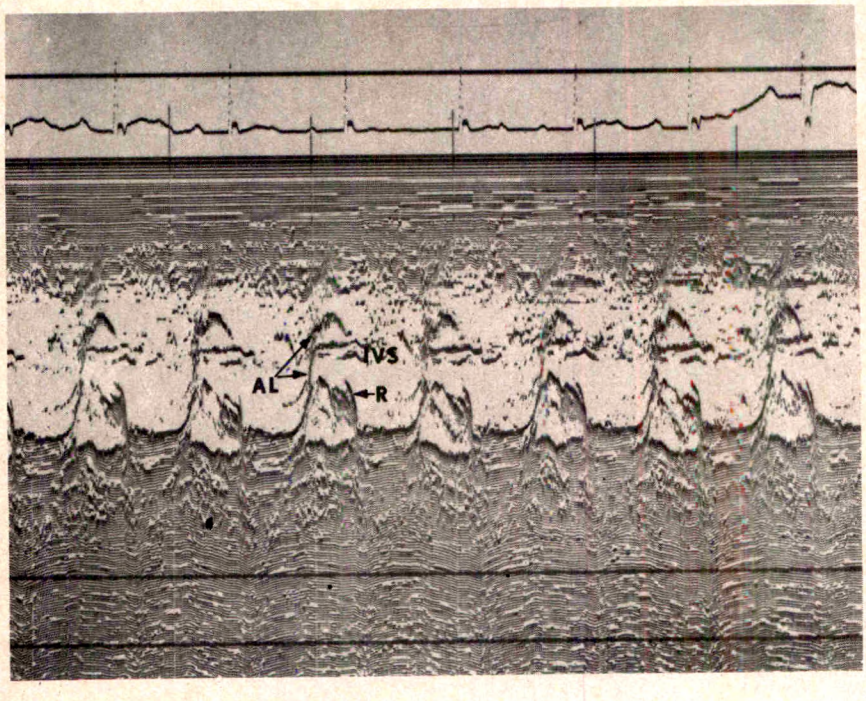

FIGURE 4. Type 4 motion. The common anterior leaflet (AL) traverses the interventricular septum (IVS) as in type 2 motion; redundancy (R) in the valve produces a double contour of anterior motion (type 4 motion).

patients with an A-V canal defect. In some patients, the common anterior leaflet does not move diagonally to the interventricular septum, whereas in others the leaflet is divided and tethered to the interventricular septum.[2,8] In addition, optimal examinations were not always possible in the children with Down's syndrome because of their erratic movements. For this reason, studies with a strip chart recorder were far more successful than earlier studies utilizing a Polaroid camera.

Complete anatomic confirmation was available in only eight patients with an A-V canal defect, at postmortem examination in five and at operation in three. A "free-floating" undivided common anterior A-V leaflet without attachment to the ventricular septum was found in five patients. In four of the five, this leaflet had been noted on ultrasonic study to traverse the ventricular septum. In the remaining three patients the A-V defect was characterized by division of the common anterior leaflet, which was usually tethered to the interventricular septum. The tricuspid contribution of the common leaflet was usually deficient and had shortened chordae tendineae. In one of the three patients, echocardiography had shown the anterior leaflet to traverse the ventricular septum. This disconcerting finding suggests that the ultrasonic spectrum of A-V canal defect may be as wide as the anatomic variations of the anterior leaflet itself.

Type 3. Abnormal tricuspid valve motion: This type of abnormal motion was registered when the transducer was aimed in the direction of the tricuspid valve and showed wide variation. The tricuspid and mitral valves were frequently recorded simultaneously in most of the patients with an A-V canal defect. Although this finding is also observed in patients with a large ventricular septal defect, it is rarely noted in patients with an atrial septal defect. The diagnostic value of this finding is somewhat limited since the abnormality is frequently observed in patients with complex congenital cardiac lesions with large ventricular communications and in those with a single ventricle.

TABLE I

Echocardiographic Differentiation of Ostium Primum Defect, Atrioventricular Canal and Ventricular Septal Defect

	OP (10)	AVC (30)	VSD (10)
Mitral-septal approximation*	70%	87%	0
Anterior mitral displacement†	90%	77%	0
Paradoxical motion of IVS‡	90%	13%	0

* Mitral E to F slope fused with the interventricular septum.
† Anterior diastolic displacement of the mitral image.
‡ Type A or B septal motion.
Figures in parentheses indicate number of patients.
AVC = atrioventricular canal; IVS = interventricular septum; OP = ostium primum defect; VSD = ventricular septal defect.

Cleft formation of the septal leaflet of the tricuspid valve splits the leaflet into two portions (Fig. 5). The anterior segment constitutes part of the common anterior A-V leaflet. This peculiar arrangement replaces the normal posterior-moving septal leaflet with an anterior-moving tricuspid component that appears to originate from the septum during diastole. It is often difficult to determine whether this motion represents a normal anterior tricuspid leaflet or a cleft septal leaflet. Two unique features differentiate the abnormal tricuspid leaflet. First, posterior movement of a tricuspid leaflet during diastole was not recorded in any of our patients with an A-V canal defect. Second, the tricuspid motion seemed to arise from the interventricular septum, frequently capping

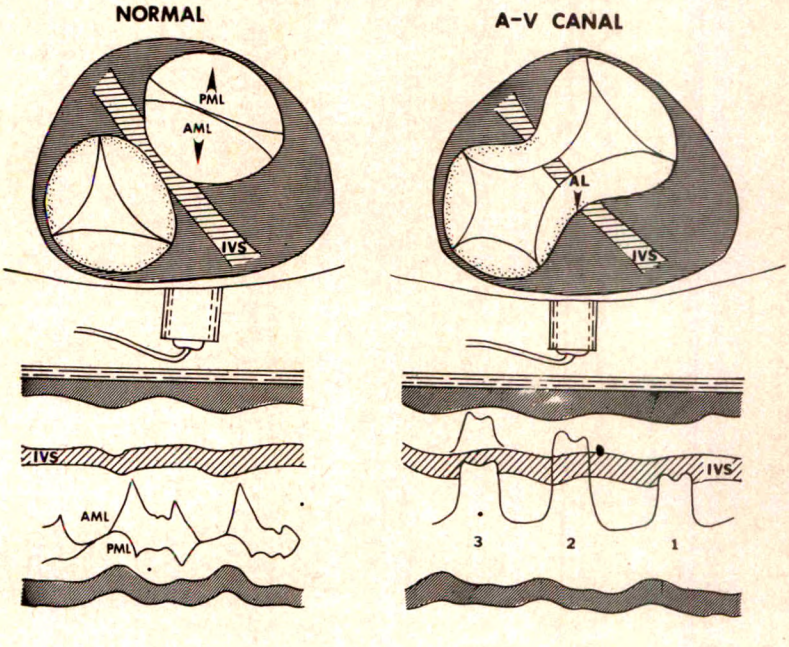

FIGURE 5. Illustration of the anatomy of the atrioventricular valves and interventricular septum (IVS) in the horizontal plane **(above)** and the corresponding echocardiogram **(below)** in the normal subject **(left)** and in the patient with atrioventricular canal **(right)**, indicating the motion **(arrows)** of the anterior (AML), posterior (PML) mitral, and the common anterior (AL) leaflets relative to the interventricular septum. Type 1, 2 or 3 motion was recorded when the transducer was focused on the respective sites.

the mitral excursion and simulating a common leaflet traversing the septum (Fig. 3). The former configuration probably represents an area on the common leaflet closer to the tricuspid component, whereas type 2 motion reflects an intermediate zone. This particular tricuspid motion can be differentiated from type 2 movement when the tricuspid valve clearly opens before the mitral valve, and the opening slopes differ (Fig. 3).

The echocardiographic excursions of the mitral and tricuspid leaflets were variable. This finding is not surprising since the relative fullness of the tricuspid and mitral components vary from one patient to another.[2–5,8]

Type 4. Double contour of the mitral leaflet in diastole: This type of abnormal motion was originally thought to represent clefts in the valve.[9] It was rarely recorded in our series and seems to be the least consistent and least reliable criterion for diagnosis.

A more useful sign was the multiple duplication of the systolic image of the mitral leaflets, which is probably due to redundancies and irregularities of the mitral valve leaflets as they attempt to merge during systole. This finding was also noted in patients with an ostium primum defect (Fig. 1). Caution should be exercised in interpreting this sign since a duplicated type of image is frequently seen in the echocardiograms of normal patients when the transducer is aimed toward the annulus. However, clefts in the mitral valve produce duplication throughout the entire left ventricular scan.

Clinical implication: The diagnosis of A-V canal defect was confirmed by cardiac catheterization in all cases in which all four types of motion were recorded. We therefore believe that the diagnosis of this lesion can be made with certainty when all four types of motion are noted on the echocardiogram. Early identification of this type of lesion is important in expediting cardiac catheterization as well as the surgical approach to a difficult repair in patients who may have conotruncal abnormalities.[8,10,11]

Acknowledgment

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Cor Triatriatum: Study of 20 Cases

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Twenty cases of cor triatriatum are reported. The diagnosis was confirmed by necropsy in 16 cases and at the time of operation in 4. The lesion occurred as an isolated anomaly in 7 cases; in 13, other associated cardiac anomalies were present. Three anatomic types of cor triatriatum were identified in the cases studied at necropsy: diaphragmatic (10 cases), hourglass (3) and tubular (3). The diaphragmatic type was also present in all four cases in which the diagnosis was confirmed at operation. Associated anomalies were found in five cases of the diaphragmatic type and in each case of the hourglass or tubular types.

In isolated cor triatriatum the clinical findings were characteristic of pulmonary venous and arterial hypertension. In two cases, one with a communication between the right atrium and the accessory left atrial chamber and one with partial anomalous pulmonary venous connection associated with cor triatriatum, the clinical findings suggested a large left to right shunt with pulmonary arterial hypertension. The clinical findings varied in the cases with associated anomalies, and it was difficult to determine the cause of disturbance of the circulation.

Cor triatriatum is an uncommon cardiac anomaly in which the accessory chamber (common pulmonary vein) communicates with the left atrium through one or more openings. When not associated with other anomalies, this entity is physiologically analogous to mitral stenosis and presents clinically as pulmonary venous obstruction of various degrees of severity depending on the size of the single or multiple openings between the accessory chamber and the left atrium. Usually, in this situation, prompt surgical correction is mandatory. When the lesion is associated with other cardiac anomalies, the clinical findings vary, the diagnosis is difficult to make and the prognosis is poor. This paper presents the spectrum of the varied anatomic structures of cor triatriatum, describes the clinical findings in this entity occurring as an isolated anomaly, and emphasizes the conditions that may be associated with it.

Material

The data in 20 cases of cor triatriatum were reviewed. The diagnosis was confirmed at necropsy in 16 patients (necropsy group) and at operation in the remaining 4 patients (surgical group). Three of the 16 patients from the necropsy group had also been operated upon.

Clinical data were available in 18 cases including each case in the surgical group. Of the 20 patients, 8 were younger than 1 year, 6 were between the ages of 1 and 5 years, and 6 were older than 5 years, 2 being adults aged 38 and 41 years, respectively; 12 patients were male, and 8 were female.

Anatomic Observations

Anatomic Types of Cor Triatriatum

Among the 16 necropsy cases studied, the accessory left atrial chamber forming cor triatriatum exhibited one of three anatomic

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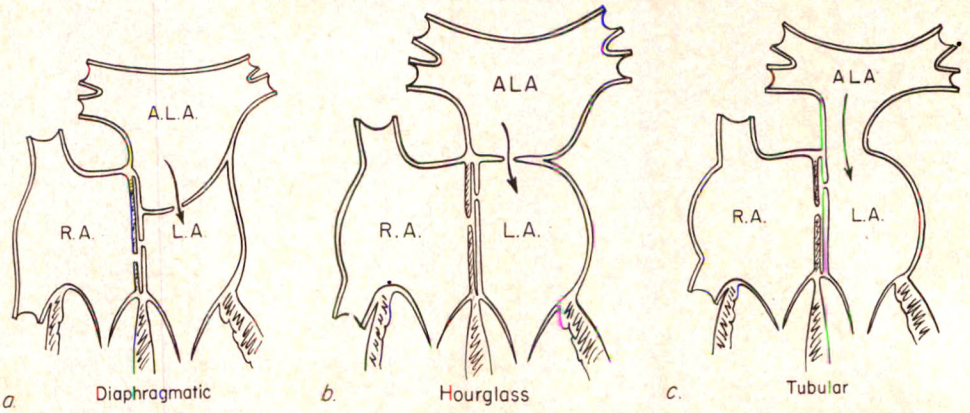
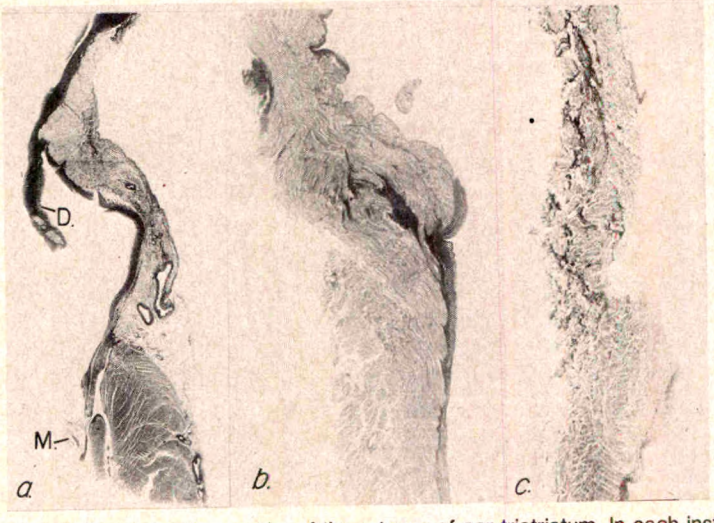


FIGURE 1. The anatomic types of cor triatriatum. **a,** diaphragmatic type. A fibromuscular diaphragm divides the left atrium into an accessory left atrial (A.L.A.) chamber and the true left atrium (L.A.). There is no external deformity. **b,** hourglass type. A constriction between the accessory left atrium and the true left atrium results in hourglass configuration as seen from the exterior of the heart. **c,** tubular type. The confluence of pulmonary veins connects with the left atrium through a tubular channel that is a persistent common pulmonary vein. R.A. = right atrium.



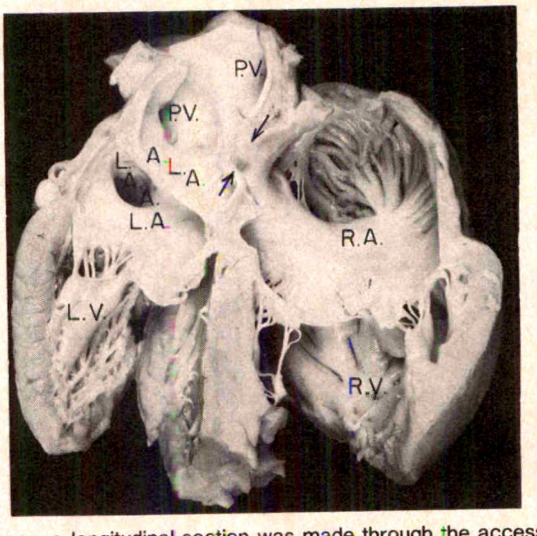


FIGURE 2 (left). Photomicrographs of three types of cor triatriatum. In each instance, a longitudinal section was made through the accessory left atrial chamber and the true left atrium. **a,** diaphragmatic type. The section has been carried through the mitral valve revealing a diaphragm (D), as well as the posterior leaflet of the mitral valve (M). Cardiac muscle is present both in the wall of the accessory left atrial chamber and in the diaphragm. **b,** hourglass type. Cardiac muscle is present both above and below the constriction representing the junction of the accessory atrium and the true left atrium. **c,** the wall of the accessory left atrial chamber appears above. Cardiac muscle is present within its wall. Elastic tissue stain ×2 **(a),** 5.4 **(b)** and 6 **(c),** reduced by 22 percent.

FIGURE 3 (right). Case 3. Interior of heart viewed from behind. The posterior walls of both atria and ventricles have been removed. A fibromuscular diaphragm divides the left atrium into an accessory chamber (A.L.A.) that receives the pulmonary veins (P.V.) and the true left atrium (L.A.). The mitral valve and the left atrial appendage (L.A.A.) communicate with the true left atrium. In this case, the anatomically sealed fossa ovalis **(between arrows)** lies against the accessory chamber. L.V. = left ventricle; R.A. = right atrium; R.V. = right ventricle.

types: the diaphragmatic (10 cases) and the hourglass and tubular types (3 cases each) (Fig. 1 and 2).

The diaphragmatic type is characterized by the presence of a diaphragm that divides the left atrium into an accessory left atrial chamber and the true left atrium (Fig. 2*a* and 3). The diaphragm is composed of thickened endocardial tissue and contains muscle fibers. There is no external evidence for the presence of the accessory chamber which, when the left atrium is opened, is observed to be dorsal, superior and medial to the true left atrium. The atrial appendage, interatrial ostium II and the mitral valve orifice communicate with the lower or true left atrial cavity. The accessory chamber receives the pulmonary veins and communicates with the true left atrium through one or more openings in the diaphragm.

In the hourglass type of cor triatriatum, a constriction is seen externally at the junction of the accessory chamber and the true left atrium (Fig. 2*b* and 4). There is no membrane within the left atrium. The left atrial appendage, interatrial ostium II and mitral valve communicate with the lower chamber.

In the tubular type, a tubular appearance is apparent on external examination (Fig. 2*c* and 5). There is no membrane. The tubular channel receives all of the pulmonary veins and can be considered a common pulmonary vein, the lower end of which joins the left atrium.

Communication between accessory chamber and left atrium and site of pulmonary venous drainage: In 9 of the 10 cases of the diaphragmatic type of cor triatriatum, the accessory chamber communicated with the true left atrial chamber through a single orifice in the diaphragm. In the 10th case, the diaphragm contained two orifices, each 2 mm in diameter. When the orifice was single, it ranged from 3 to 15 mm in diameter. It was 3 mm wide in four specimens and 4 mm, 8 mm and 15 mm wide in one specimen each. In two specimens, the size of the orifice was not measured before dissection of the membrane.

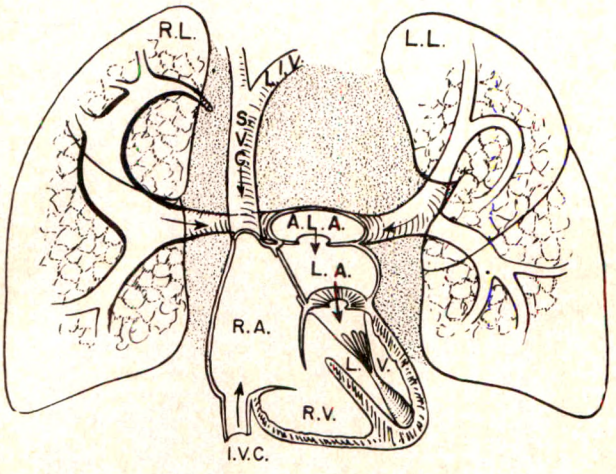


FIGURE 4 (above). Case 11. Hourglass type of cor triatriatum. The right upper pulmonary vein descends within the substance of the lung to join the right lower pulmonary vein. The latter and the veins of the left side join the accessory left atrial chamber. In addition, there was a supravalvular ring in the left atrium and a parachute mitral valve. I.V.C. = inferior vena cava; L.I.V. = left innominate vein; L.L. = left lung; R.L. = right lung; S.V.C. = superior vena cava. Other abbreviations as in Figure 3.

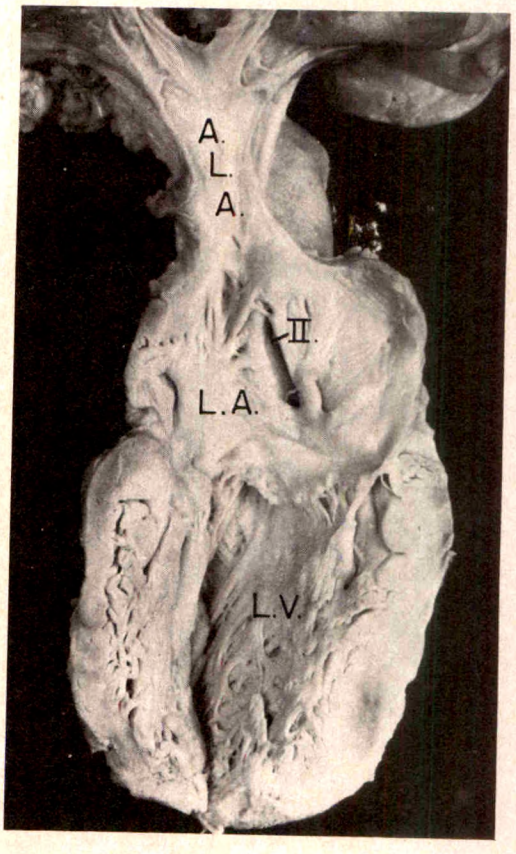


FIGURE 5 (right). Case 14. Tubular type of cor triatriatum and interior of the left atrium and the left ventricle. A tubular channel runs from the confluence of the pulmonary veins to the left atrium. The interatrial ostium II lies in the true left atrium.

In 8 of the 10 specimens of the diaphragmatic type of cor triatriatum, all of the pulmonary veins connected with the accessory chamber. In one of the remaining cases (Case 10), the right upper pulmonary vein joined the right superior vena cava, whereas the other pulmonary veins connected with the accessory left atrial chamber. In the other case (Case 1), the left pulmonary veins joined to form a single vein that connected with the left innominate vein through a vertical vein, and the right pulmonary veins connected with the accessory chamber.

In each of the three cases of the hourglass type of cor triatriatum, there was a single orifice between the accessory chamber and the true left atrium. The diameter of the opening was 6 mm in the first case (Case 11) and 7 mm in the second case (Case 12). In the third case (Case 13), the orifice had been surgically enlarged and its natural diameter is not known. In two of the three specimens with the hourglass type, the entire pulmonary venous drainage was into the accessory left atrium. In one of these, the usual pulmonary veins were present. In the other case (Case 11), the right upper pulmonary vein did not leave the lung but descended within the substance of the right lung to join the right lower vein which, in turn, joined the accessory chamber (Fig. 4) (case previously reported[1]).

In the third specimen (Case 13), described in a previous report,[2] partial anomalous pulmonary venous connection was present. In this case, each of the pulmonary veins from the left lung and the middle pulmonary vein of the right lung connected anomalously with the left innominate vein through a vertical vein. The right upper and lower pulmonary veins joined the accessory chamber, which was hypoplastic.

In each of the three cases of the tubular type, the accessory chamber communicated with the true left atrium through one opening. The communication was obstructive (diameter 3 mm) in one specimen and wide and nonobstructive in the other two specimens. In the case with obstruction and in one of the two without obstruction, all of the pulmonary veins connected to the accessory chamber. In the other specimen without obstruction (Case 16), the upper lobe veins of both lungs joined the true left atrium whereas the lower lobe veins of each side joined the accessory chamber.

Relation of Fossa Ovalis with Left Atrial Chambers

The fossa ovalis had a variable relation with the accessory chamber and true left atrial cavity in the 16 necropsy cases of cor triatriatum. The fossa ovalis lay between the true left and right atria in all six specimens with the hourglass and tubular types of cor triatriatum. In four of these, the foramen ovale showed valvular competent patency, and in two there was an atrial septal defect.

Of the 10 cases with the diaphragmatic type, one exhibited a valvular competent patent foramen ovale, the communication being between the right atrium and the true left atrium. In two patients, a secundum atrial septal defect was present. In each, the communication lay between the right atrium and the true left atrium. The fossa ovalis was identified in five of the remaining seven patients. In two, the fossa ovalis was opposite the true left atrium; in the other three,

TABLE I

Anatomic Findings

Case no.	Age & Sex	Anomalous Pulmonary Venous Connection	Atrial Septal Defect	Associated Anomalies
			A. Diaphragmatic Type	
1	7 mo, F	Left pulmonary veins to left innominate vein	0	None
2	14 mo, M	0	0	None
3	21 mo, M	0	0	None
4	3 yr, F	0	0	None
5	7 mo, F	0	Accessory chamber to right atrium	None
6	7 yr, M	0	0	Hurler's syndrome; thickening of all cardiac valves, coronary and abdominal vessels
7	38 yr, F	0	Fossa ovalis ASD between left atrium and right atrium	Ebstein's anomaly; bicuspid stenotic pulmonary valve
8	41 yr, F	0	Absent atrial septum	Transitional atrioventricular canal; left superior vena cava to coronary sinus
9	2 mo, F	0	Fossa ovalis ASD between left atrium and right atrium	Mitral atresia; hypoplastic ascending aorta and arch; coarctation; bicuspid aortic valve; anomalous right subclavian artery; PDA; VSD; atresia of right atrial ostium of coronary sinus
10	7 mo, M	Right upper lobe pulmonary vein to right superior vena cava	Inferior to fossa ovalis	Partial atrioventricular canal; accessory orifice mitral valve; PDA; left superior vena cava to coronary sinus; bicuspid pulmonary valve
			B. Hourglass Type	
11	7 yr, M	Right upper lobe pulmonary vein to right lower lobe pulmonary vein	0	Coarctation; tubular hypoplasia of arch; VSD; supravalvular ring of left atrium; parachute mitral valve
12	3 mo, F	0	0	Corrected transposition with isolated bulbar inversion; VSD; left juxtaposition of appendages; subaortic stenosis; left superior vena cava to coronary sinus
13	1 1/2 yr, M	Right middle lobe and left pulmonary veins to left innominate vein	0	Coarctation of aorta
			C. Tubular Type	
14	3 mo, F	0	Fossa ovalis ASD between left and right atria; ASD site of coronary sinus	Tetralogy of Fallot; bicuspid pulmonary valve; absent coronary sinus; left superior vena cava to left atrium
15	4 mo, M	0	0	VSD; right aortic arch; right-sided PDA
16	1 day, M	Upper pulmonary veins to true left atrium; lower pulmonary veins to accessory left atrium	Fossa ovalis ASD between left and right atria	Aortic atresia; mitral atresia; PDA; hypoplastic ascending aorta; coarctation

ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

it was opposite the accessory left atrium. In one of the remaining two specimens an ostium primum atrial septal defect was present between the right atrium and the true left atrium, and the fossa ovalis was not identified. In the other, the atrial septum was absent, allowing communication between the right atrium and the true left atrium.

Interatrial Communication

Among the total of 16 specimens of cor triatriatum, 11 showed some type of interatrial communication. In four a valvular competent patent foramen ovale was present and allowed right to left communication between the right atrium and true left atrium. In the remaining seven a through-and-through defect was present in the septal wall of the right atrium. In four of the latter, the defect was at the fossa ovalis and lay between the right atrium and the true left atrium. In the fifth case with a defect (diaphragmatic type, Case 5), the defect had been completely closed at operation. On the basis of clinical and pathologic features, it was clear that this defect had been between the accessory chamber and the right atrium. In the sixth and seventh cases with defects (each with the diaphragmatic type of cor triatriatum), persistent common atrioventricular canal was associated. In one of

these, there was the classic persistent ostium primum; the other was the aforementioned case of absence of the atrial septum.

Associated Anomalies

Anomalies additional to those mentioned were present in 11 of the 16 necropsy cases. No examples of asplenia or polysplenia were encountered. These associated anomalies were seen in 5 of the 10 cases of the diaphragmatic type and in each of the 6 cases of the hourglass or tubular type (Table I).

Commonly associated anomalies were ventricular septal defect (five cases), coarctation of the aorta (four cases) and persistent common atrioventricular canal (two cases).

The unusual associated anomalies, occurring in one case each, were tetralogy of Fallot, Ebstein's anomaly of the tricuspid valve (previously reported[3]), and isolated bulbar inversion with corrected transposition of the great vessels (previously reported[4]). To our knowledge, no other cases of cor triatriatum associated with Ebstein's anomaly or corrected transposition have been reported. The association with tetralogy of Fallot is also rare and our case is the sixth case of such a combination.[5]

Clinical Observations

Clinical and laboratory data were available in 18 cases, 14 from the necropsy group and 4 from the surgical group. These 18 cases can be classified into three groups: (1) The first consists of seven cases (three from the necropsy group; four from the surgical group) in which cor triatriatum was the only anomaly. (2) The second group consists of two cases, each from the necropsy group, with a low pressure left to right shunt proximal to the true left atrium. In one (Case 5), there was a defect between the accessory left atrium and the right atrium. In the other (Case 1) the left pulmonary veins joined the left innominate vein, whereas the right pulmonary veins joined the accessory left atrium. (3) The third group consists of nine cases (all from the necropsy group) with various complex anomalies. Since these associated anomalies dominated the clinical presentation, it does not seem fruitful to analyze the clinical and related features in these cases. The material to follow will therefore concern itself only with examples of cor triatriatum occurring alone or in association with an atrial septal defect or partial anomalous pulmonary venous connection.

Isolated Cor Triatriatum

Of the seven patients with uncomplicated cor triatriatum, three were from the necropsy group and were aged 14 months, 21 months and 3 years, respectively, at the time of death. The four patients in the surgical group without associated anomalies had been operated on successfully at the ages of 4, 5, 17 and 24 years, respectively.

All seven patients were dyspneic. Two patients gave a history of cyanosis and three of frequent pulmonary infections. Six patients presented with congestive cardiac failure and one with syncopal attacks.

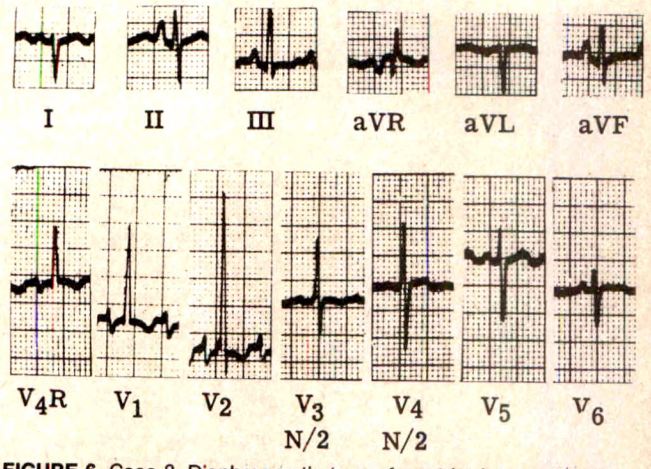


FIGURE 6. Case 3. Diaphragmatic type of cor triatriatum without associated anomalies. The electrocardiogram shows signs of right atrial and ventricular hypertrophy. N/2 = half standardization.

Physical examination disclosed a normal first cardiac sound in all seven patients. The second sound, adequately described in six patients, was split with accentuation of the pulmonary component. A systolic ejection murmur ranging in intensity from grade 1–3/6 was present in four patients and associated with a thrill in one. The maximal intensity of the murmur was along the left sternal border. A holosystolic murmur, grade 3/6, associated with a thrill was present in one patient. An early diastolic murmur with maximal intensity along the left sternal border was noted in two patients, and a mid-diastolic murmur in one. Two patients had no murmur. A mitral opening snap was not present in any of the cases.

The electrocardiogram disclosed a frontal plane QRS axis ranging from +100° to +120°. Isolated right atrial hypertrophy was present in three patients, and combined right and left atrial hypertrophy in two. The QRS duration was normal, and signs of right ventricular hypertrophy were present in each case (Fig. 6).

Chest roentgenogram revealed a normal cardiac size in one patient and cardiomegaly in six patients, of mild degree in five and of moderate degree in one. There was no evidence of left atrial enlargement. All seven had features of pulmonary venous congestion and pulmonary arterial hypertension (Fig. 7).

Cor Triatriatum and Left to Right Shunt Proximal to True Left Atrium

Defect between the accessory left atrium and the right atrium. In this situation there is a large, left to right shunt from the accessory left atrium to the right atrium. In our series, there was one such case (Case 5). The patient was 7 months of age at the time of death. The presenting features were dyspnea and congestive cardiac failure. The physical findings were those of a large left to right shunt at the atrial level (the detailed findings of this case have been reported earlier[6]). The electrocardiogram disclosed a mean frontal plane QRS axis of −90° with biatrial

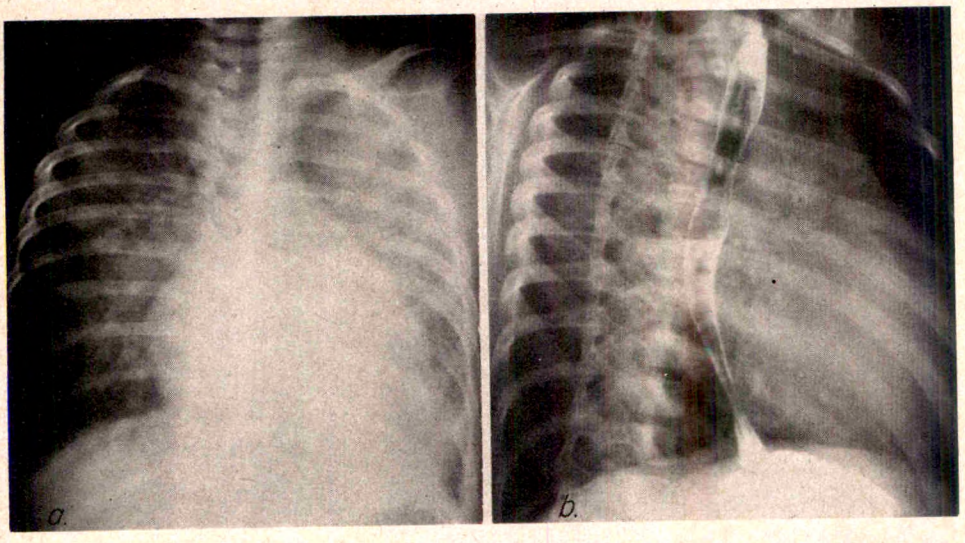


FIGURE 7. Case 2. Cor triatriatum of the diaphragmatic type without associated anomalies. Frontal **(a)** and lateral **(b)** views of chest roentgenogram. Pulmonary congestion is evident. The esophagus is not significantly distorted.

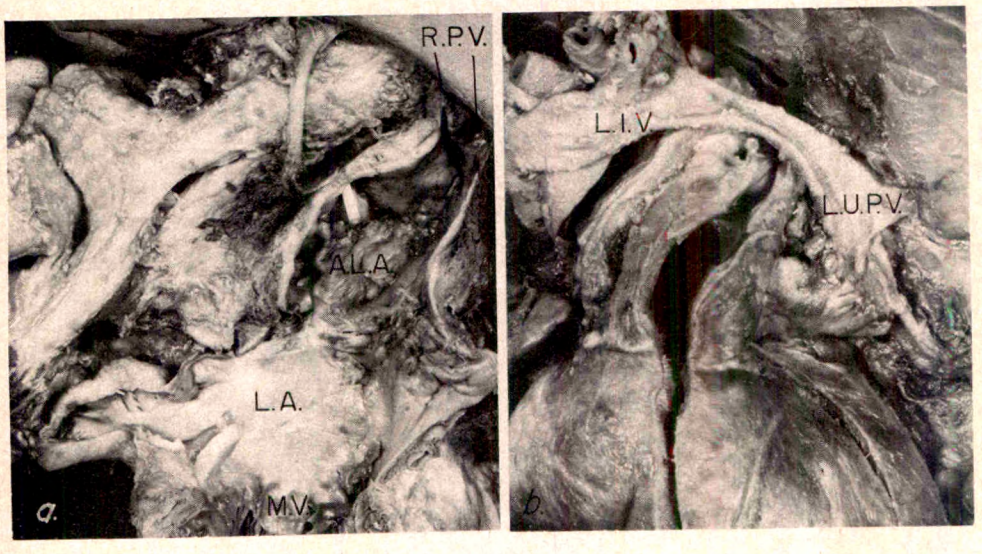


FIGURE 8. Case 1. Diaphragmatic type of cor triatriatum with anomalous connection of the left pulmonary veins to the left innominate vein. **a,** interior of accessory left atrium, true left atrium and a portion of the mitral valve. The right pulmonary veins join the accessory left atrial chamber. The diaphragm has been surgically resected. **b,** the left upper pulmonary vein receives veins from the lower lobe of the left lung, as well as from the upper lobe. This has been anastomosed to the left atrial appendage. An anomalous vertical vein courses from the left upper pulmonary vein to the left innominate vein. A.L.A. = accessory left atrium; L.A. = true left atrium; L.I.V. = left innominate vein; L.U.P.V. = left upper pulmonary vein; M.V. = mitral valve; R.P.V. = right pulmonary vein.

and right ventricular hypertrophy. The chest roentgenogram revealed generalized cardiomegaly and increased pulmonary vasculature.

Cor triatriatum with partial anomalous pulmonary venous connection: This lesion was seen in one case (Case 1). The cor triatriatum was of the diaphragmatic type. The right pulmonary veins joined the accessory left atrium, but the left pulmonary veins terminated through a vertical vein in the left innominate vein (Fig. 8).

The patient was a female infant who died at age 7 months. Congestive cardiac failure was the presenting manifestation. The first cardiac sound was normal. The second sound was split with accentuation of the pulmonary component. The electrocardiogram disclosed a mean frontal plane QRS axis of +150° with right atrial hypertrophy and right ventricular hypertrophy. The chest roentgenogram revealed generalized cardiomegaly and increased pulmonary vasculature. There was no difference between the vasculature of the right and left lungs although there was significant obstruction in the diaphragmatic membrane between the accessory and true left atrium. Angiocardiographic studies identified the anomalous pulmonary venous connection (Fig. 9). The patient died after resection of the left atrial membrane and anastomosis of the anomalous vertical vein to the left atrial appendage.

Cardiac Catheterization and Angiocardiographic Observations

Cardiac catheterization and angiocardiographic studies were available in four cases of isolated cor triatriatum. In the single case with a communication between the right atrium and the accessory left atrium, limited cardiac catheterization studies were available (Table II).

In three of the four cases of isolated cor triatriatum, marked pulmonary arterial hypertension and increased pulmonary arterial wedge pressures were found. In the fourth case, the pressures were mildly elevated. Each of these patients was operated upon, and two underwent postoperative studies. In one of these (Case 17), the postoperative pressures were normal. In the other (Case 20), studies performed 9 years after operation showed an increase in pressure over preoperative values. At the first operation the

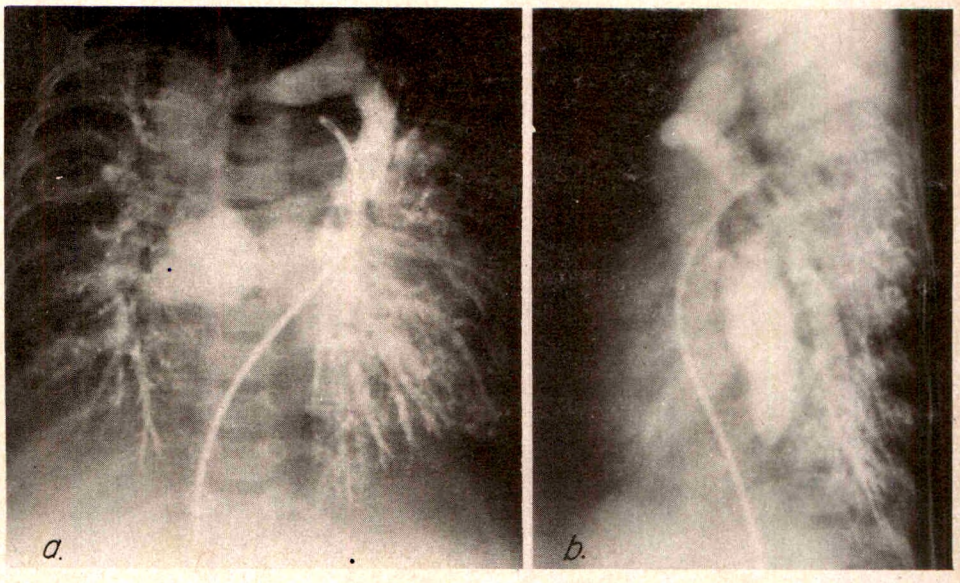


FIGURE 9. Case 1. Levophase of pulmonary arteriogram showing opacification of the accessory left atrial chamber by blood entering from the right pulmonary veins. Blood from the left pulmonary veins joins an anomalous vertical vein that terminates in the left innominate vein. **a,** frontal view. **b,** lateral view.

TABLE II

Cardiac Catheterization Data

Case no.	Age & Sex	Pressures (mm Hg)							
		Right Atrium	Right Ventricle	Pulmonary Artery	Pulmonary Artery Wedge	Systemic Artery	Left Ventricle	Accessory Left Atrium	Left Atrium
A. Isolated Cor Triatriatum									
17									
Before operation	4 yr, F	(6)	85/5	85/34 (60)	(35)	...	...	...	...
After operation	5 yr, F	(6)	39/3	34/12 (20)	(8)	...	...	...	...
18	5 yr, M	...	90/6	90/45 (70)	(22)	...	...	...	...
19	17 yr, M	(4)	68/1–5	68/40 (50)	(40)	96/60	...	...	...
20									
Before operation	24 yr, F	...	35/3	35/15 (23)	...	...	...	...	...
After first operation	34 yr, F	...	82/2	82/44 (56)	(26)	...	97/6	...	...
After second operation	35 yr, F	...	...	22/14 (18)	(8)	...	...	...	...
B. Cor Triatriatum with Communication Between Accessory Left and Right Atria									
5*	7 mo, M	(5)	85/10	...	...	...	90/0-13	$a = 17$ (7)	(7)

* Eighty-nine percent left to right shunt at the atrial level.
Figures in parentheses indicate mean pressures.

opening in the membrane between the two left atrial components had been enlarged. When this patient was reoperated upon, the membrane separating the accessory chamber and the true left atrium was resected. After this procedure, the pulmonary arterial and pulmonary arterial wedge pressures were normal.

In the patient with a communication between the right and the accessory left atrium (Case 7), limited studies were performed, revealing elevated right ventricular pressure with a large left to right shunt at the atrial level.

Pulmonary arteriograms were obtained in each of the four cases in the surgical group with isolated cor triatriatum. In each, there were features indicating obstruction at or near the mitral valve. In none, however, could the membrane or accessory chamber be clearly identified.

Discussion

Incorporation of the common pulmonary vein into the left atrium begins at about the 5th week of embryonic life.[7,8] There is common agreement that cor triatriatum results from failure of absorption of the common pulmonary vein into the left atrium, the accessory left atrial chamber representing the common pulmonary vein. Arrest in the normal process may occur at different stages of the growing embryo so that persistence of the common pulmonary vein may yield a variable structure.

Anatomic variations: In our series of cases, three anatomic types of cor triatriatum were identified: the classic diaphragmatic, hourglass and tubular types. The tubular type appears to be the most primitive form, since the accessory chamber retains a vessel-like shape.

On hypothetical grounds, the fossa ovalis would be expected to lie against the wall of the true rather than the accessory left atrial chamber. In our cases, as in those of others,[9] the position of the fossa ovalis showed some variation. In each of our cases with the hourglass or tubular structure, the fossa ovalis lay between the right atrium and the true left atrium. In the diaphragmatic type of cor triatriatum, the position of the fossa ovalis varied. When there was no defect in the atrial septum, it was difficult to determine whether a defect, if present, would have communicated with the true left atrium or the accessory left atrium. When an atrial septal defect was present, it allowed communication between the true left atrium and the right atrium in six cases, and between the accessory left atrium and right atrium in one case.

In the majority of cases of cor triatriatum, the pulmonary veins join the accessory left atrium. It is understandable, nevertheless, that anomalous pulmonary venous connection may occur since, although primitive venous channels are still present in the embryo, an obstructive connection between the common pulmonary vein and the left atrium may result in the preservation of primitive connections so that the pulmonary veins may join systemic veins.[10–12] Total or partial anomalous venous connection may be associated with cor triatriatum. But when there is total anomalous pulmonary venous connection, the cases are usually identified not as cor triatriatum but as examples of total anomalous pulmonary venous connection. Four of our cases showed partial anomalous pulmonary venous connection.

Anomalies associated with cor triatriatum were common in our series. A defect in the atrial septum was present in 7 of the 16 cases in the necropsy group. Only one of the defects was between the right atrium and the accessory left atrial chamber.

Clinical features: In cases of isolated cor triatriatum, the severity of the clinical findings was related to the degree of obstruction produced by the stenotic orifice or orifices between the accessory left atrium and the true left atrium. All of our patients gave a history of dyspnea, and three died before age 2 years. Although murmurs were frequently noted, they were nonspecific and variable in time, quality and location. An accentuated pulmonary component of the second sound was the only consistent auscultatory finding. Mild to moderate cardiomegaly with prominent pulmonary vascular markings was a constant radiologic finding. No patient had evidence of left atrial enlargement. Right axis deviation of the mean QRS axis at the frontal plane and right ventricular hypertrophy were the typical electrocardiographic findings. All cases except one in which cardiac catheterization was performed manifested severe pulmonary hypertension and markedly elevated pulmonary arterial wedge pressure. Selective pulmonary arteriograms allowed the confirmation of obstruction at or near the mitral valve.

Associated anomalies: The clinical profile of cor triatriatum was significantly modified when associated anomalies were present. In one case wherein cor triatriatum was associated with a communication between the accessory chamber and the right atrium, the clinical findings mimicked those of Lutembacher's syndrome in which significant left to right shunting is present at the atrial level. In the case with isolated cor triatriatum and partial anomalous pulmonary venous connection, the clinical presentation of severe pulmonary hypertension was interpreted as secondary to the left to right shunt. In the remaining cases wherein cor triatriatum was associated with other cardiac anomalies, it was difficult to be sure which was the more direct determinant of the hemodynamic changes.

Surgical results: Four of the patients with isolated cor triatriatum were operated upon; in three, the membrane was excised. Postoperative studies, performed in one of these patients, revealed normal hemodynamic values.

In one patient the orifice of the membrane was enlarged and postoperative studies 9 years later disclosed persistence of the hemodynamic abnormalities. Excision of the membrane at reoperation resulted in normal hemodynamic values. This experience emphasizes that excision of the membrane between the accessory and true left atria is the crucial step in surgical cure.

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Clinical Implications of Warfarin Interactions with Five Sedatives

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The intensity, uniformity and time course of anticoagulant interference by phenobarbital, secobarbital, glutethimide, chloral hydrate and methaqualone were systematically investigated in 16 patients receiving coumarin therapy. Each subject received an individualized fixed daily dose of warfarin and served as his own pre- and postsedative treatment control. Prothrombin times were measured four times weekly during five long-term experiments. Anticoagulant inhibition was observed during the administration of phenobarbital, secobarbital and glutethimide; there was no significant change in prothrombin test results during the trials of chloral hydrate and methaqualone. Barbiturates and glutethimide should not be administered to patients receiving coumarin drugs. The concurrent use of drugs from these groups is decreasing according to a survey of 200 hospital medical records. Chloral hydrate and methaqualone interact pharmacologically with orally administered anticoagulant agents, but the effect is not clinically significant. It is concluded that chloral hydrate and methaqualone may be administered safely without additional caution in prothrombin test monitoring during oral anticoagulant therapy.

Interactions between coumarin anticoagulant agents and certain sedatives are potentially important because of the frequent concurrent administration of these drugs[1,2] and the magnitude of anticoagulant interference that may result.[3–5] Because of anxiety and insomnia associated with serious cardiovascular diseases, sedative and hypnotic agents are frequently prescribed for patients receiving anticoagulant treatment, and an exact identification of each sedative that may inhibit or potentiate coumarin therapy should be established. The interacting mechanism, intensity and uniformity of anticoagulant interference, speed of onset and dissipation of action, and clinical significance of each coumarin-sedative interaction should be determined and this knowledge disseminated widely to all physicians administering oral anticoagulant agents.

The barbiturates[1–10] and glutethimide[11–14] have been shown to inhibit the action of coumarin drugs, whereas chloral hydrate has been reported to inhibit,[15] potentiate mildly[16,17] or exert no effect[14,18,19] on therapeutic hypoprothrombinemia. The present study involved a systematic investigation in man of the intensity, uniformity and time course of anticoagulant interference by phenobarbital, secobarbital, glutethimide, chloral hydrate and methaqualone in doses commonly used for sedation during long-term warfarin therapy.

Methods and Materials

A study pool of 17 subjects, 16 men with various cardiovascular diseases and 1 healthy man, ranging in age from 34 to 78 years, participated in five experiments that extended over 18 months. The Quick prothrombin test was performed in duplicate four times weekly with use of a fibrometer and commercial rabbit brain thromboplastin. An individualized dose of sodium war-

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farin, ranging from 17.5 to 77.5 mg/week, was established for each patient; this dose produced prothrombin times of 18 to 22 seconds. Once determined, this warfarin dose was not changed in any subject throughout these experiments. Patients were selected at random from the study pool in groups of 10 for each experiment. After a 4 week pretrial period of warfarin therapy alone, each patient continued to receive warfarin and also ingested phenobarbital, 0.1 g, at bedtime each night for 4 weeks; this period was followed by a 4 week post-trial period in which the patient again received only warfarin therapy. This experiment was repeated sequentially with secobarbital, 0.1 g, chloral hydrate, 0.5 g, glutethimide (Doriden®), 0.5 g, and methaqualone (Quaalude®), 0.3 g, with a rest period of at least 2 weeks between each experiment.

No patient took any other drug known to interact with warfarin. All subjects completed each trial entered and none had hemorrhages or other complications. The Student t test for paired observations was used in a statistical analysis of the data to determine the P values for the differences in the average prothrombin time before and during, and before and after each sedative drug was given.

Results

The data consisted of prothrombin times measured four times weekly in 10 volunteers who received fixed daily doses of warfarin before, during and after the administration of five sedatives in separate trials. The average prothrombin time was significantly reduced during administration of phenobarbital, secobarbital and glutethimide, and slightly but not significantly reduced during administration of methaqualone. There was no change during the trial of chloral hydrate (Table I).

Warfarin inhibition was observed in 9 of 10 patients, respectively, in each experiment before or within 2 weeks after the administration of phenobarbital, secobarbital or glutethimide (Table II, Fig. 1 to 3). There was little or no effect during the 1st week of each sedative trial. The intensity of anticoagulant inhibition by phenobarbital and glutethimide was approximately equal, somewhat greater than the intensity of inhibition induced by secobarbital. The duration of inhibition was more prolonged after the discontinuation of glutethimide therapy than during ad-

TABLE I

Variance of Mean Prothrombin Times for All Subjects

Sedative	Bedtime Dose (g)	Mean Prothrombin Time (sec) Pre-trial	Trial	P Value*	Post-trial	P Value†
Phenobarbital	0.1	19.6	17.0	0.005	18.4	NS
Secobarbital	0.1	19.7	18.3	0.02	18.0	0.02
Chloral hydrate	0.5	18.9	19.3	NS	19.2	NS
Glutethimide	0.5	18.8	16.5	0.01	16.1	0.001
Methaqualone	0.3	20.9	20.4	NS	19.6	NS

* Trial versus pretrial.
† Post-trial versus pretrial.
NS = not significant.

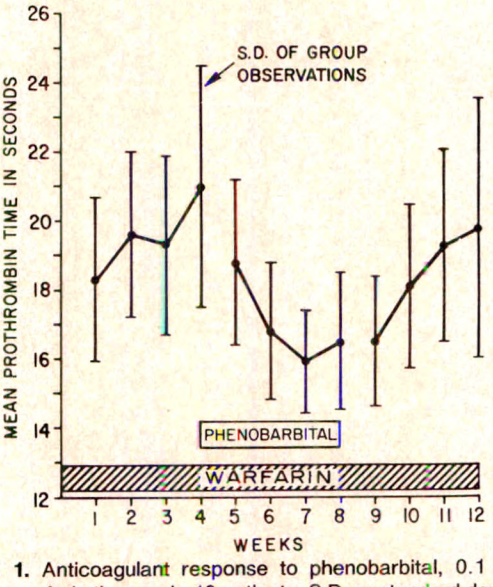

FIGURE 1. Anticoagulant response to phenobarbital, 0.1 g daily, added to warfarin therapy in 10 patients. S.D. = standard deviation.

TABLE II

Average Weekly Prothrombin Times During the Phenobarbital Study

Case no.	Pretrial 1	2	3	4	Trial 5	6	7	8	Post-Trial 9	10	11	12
1	18.3	20.8	17.9	18.8	18.4	15.2	15.0	13.4	14.5	19.3	19.4	19.9
2	22.8	20.8	22.2	23.1	20.3	17.0	17.0	17.6	17.7	18.3	21.9	20.8
3	17.1	19.8	19.8	20.0	16.0	16.8	15.2	16.2	15.4	20.2	20.0	18.1
4	16.4	17.4	16.1	16.9	16.2	14.6	13.9	15.1	14.5	14.5	14.3	14.6
5	16.3	16.6	16.0	17.8	16.7	17.8	16.1	17.1	18.7	21.7	20.7	18.2
6	16.6	16.8	16.9	15.9	16.3	14.6	15.0	13.4	13.7	13.7	14.3	14.6
7	16.4	20.2	19.7	25.6	20.9	17.7	15.4	19.5	17.4	19.5	22.8	25.9
8	22.4	25.4	24.5	26.5	20.9	21.0	18.4	17.7	19.6	19.0	22.3	26.2
9	16.7	19.4	20.8	22.4	23.5	19.1	18.6	18.5	17.1	16.2	19.1	20.0
10	19.9	18.6	19.2	22.5	18.5	14.6	14.6	...	16.2	18.4	18.5	19.3
Average	18.3	19.6	19.3	21.0	18.8	16.8	15.9	16.5	16.5	18.1	19.3	19.8
±SD	±2.4	±2.4	±2.6	±3.5	±2.4	±2.0	±1.5	±2.0	±1.9	±2.4	±2.8	±3.8

SD = standard deviation.

TABLE III

Average Weekly Prothrombin Times During the Chloral Hydrate Study

Case no.	Pretrial				Trial				Post-Trial			
	1	2	3	4	5	6	7	8	9	10	11	12
1	18.6	16.4	16.2	16.8	16.3	17.2	18.1	18.9	18.2	18.9	18.4	16.3
2	24.9	23.2	20.4	19.4	21.9	23.1	22.1	21.4	22.0	23.2	24.0	19.4
3	19.6	19.3	18.1	19.5	20.0	18.3	19.1	18.3	19.7	19.3	20.2	18.7
4	19.2	18.7	18.4	18.0	19.7	18.0	19.2	19.8	19.4	18.4	18.8	17.7
5	19.8	15.2	15.0	17.4	20.1	18.4	17.6	18.1	17.3	18.1	18.9	18.6
6	21.3	19.3	20.0	20.0	18.9	18.9	18.7	20.0	19.4	19.8	19.9	19.4
7	18.2	18.7	18.7	17.8	18.4	18.1	19.8	19.1	19.0	18.4	18.7	19.6
8	18.2	18.7	19.1	19.1	19.0	18.8	18.7	19.2	18.3	18.3	18.3	18.6
9	18.5	18.8	19.1	19.5	19.0	18.4	19.4	20.1	18.4	20.1	19.8	18.5
10	19.1	20.2	17.5	19.5	20.8	21.2	18.0	21.7	19.1	20.0	18.3	20.1
Average	19.7	18.9	18.3	18.7	19.4	19.0	19.1	19.7	19.1	19.5	19.5	18.7
±SD	±1.9	±2.0	±1.6	±1.0	±1.4	±1.7	±1.2	±1.1	±1.2	±1.4	±1.6	±1.0

SD = standard deviation.

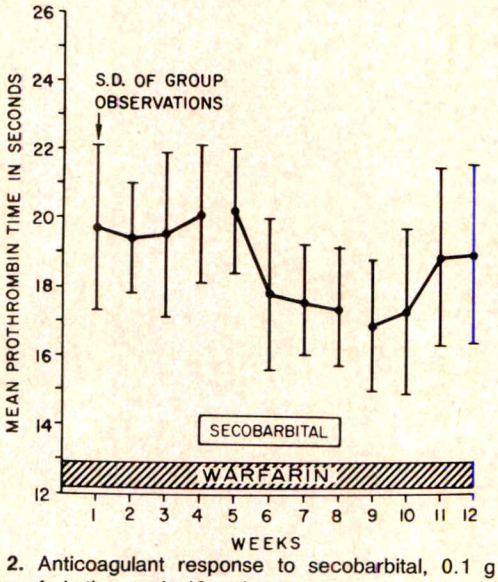

FIGURE 2. Anticoagulant response to secobarbital, 0.1 g daily, added to warfarin therapy in 10 patients.

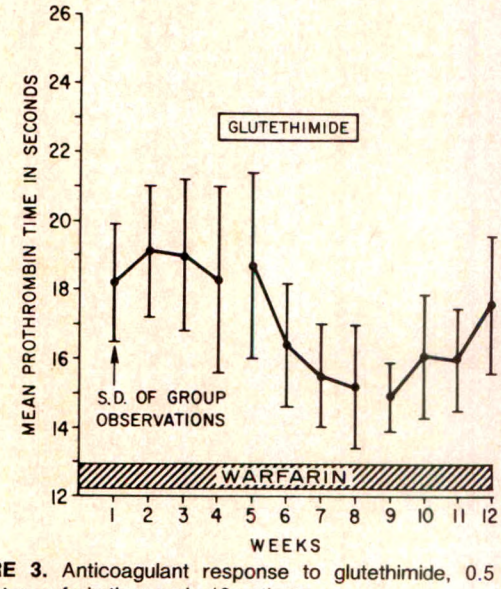

FIGURE 3. Anticoagulant response to glutethimide, 0.5 g daily, added to warfarin therapy in 10 patients.

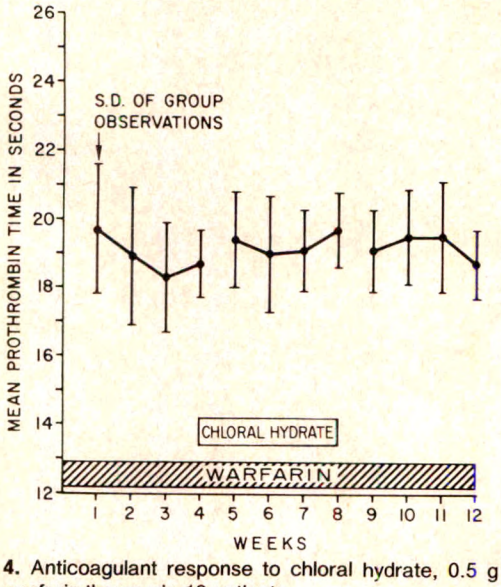

FIGURE 4. Anticoagulant response to chloral hydrate, 0.5 g daily, added to warfarin therapy in 10 patients.

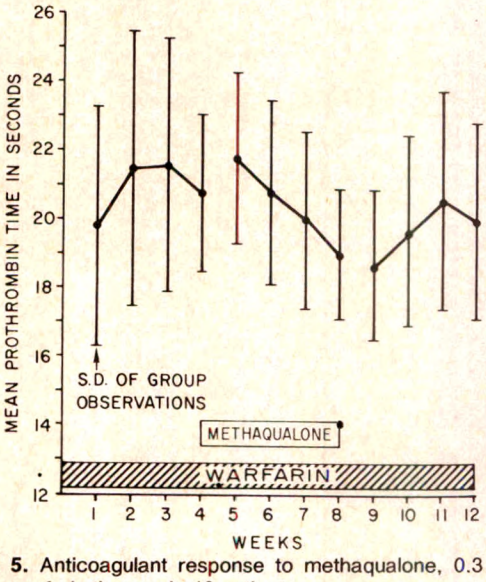

FIGURE 5. Anticoagulant response to methaqualone, 0.3 g daily, added to warfarin therapy in 10 patients.

ministration of either barbiturate. Average prothrombin times returned to pretreatment levels by the 3rd and 4th weeks, respectively, after discontinuation of barbiturate and glutethimide therapy.

By contrast, there was no significant change in average prothrombin time during or after the administration of chloral hydrate (Table III, Fig. 4). Four patients had a very small rise in prothrombin time (averaging 2 seconds more than values in the last week of the pretrial) during the 1st week of chloral hydrate therapy, but the 12 week results for these four patients as well as the other six were not significantly different. A mild anticoagulant inhibitory action was noted during and shortly after the administration of methaqualone, but the intensity did not reach statistical significance (Table I, Fig. 5).

Discussion

The results of these experiments confirm earlier reports that phenobarbital,[2,4–11,12,14] secobarbital[3,6,13,20] and glutethimide[11–14] inhibit warfarin-induced hypoprothrombinemia significantly in man, whereas chloral hydrate[14,18,19] and methaqualone[21] do not. My studies provide a systematic assessment of the anticoagulant inhibitory action of two barbiturates and glutethimide in human volunteers and supports recent evidence that chloral hydrate does not interfere with oral anticoagulant therapy in a clinically significant manner.

Barbiturates

Barbiturate inhibition of oral anticoagulant therapy, first recognized 2 decades ago in South America,[6] results from an increased synthesis (induction) of hepatic microsomal enzymes that accelerate the metabolism of coumarin drugs.[9,10,22] This drug interaction has been documented conclusively in eight studies involving 96 patients[1,4,5,7–10,14] treated with long- and short-acting barbiturates. The studies reported here suggest that phenobarbital is a more potent enzyme inducer than is secobarbital, although MacDonald[14] and Robinson[20] and their associates found that phenobarbital, secobarbital, amobarbital and glutethimide had the same magnitude of pharmacologic action. Approximately 90 percent of all patients receiving coumarin drugs respond to the enzyme-stimulating activity of the barbiturates with decreased hypoprothrombinemia, but important individual differences exist and the increased anticoagulant dosage required by individual patients cannot be predicted upon the administration of a barbiturate.

MacDonald and Robinson[2] established the clinical significance of barbiturate interference with anticoagulant therapy; enzyme induction appeared to be a factor in 14 bleeding complications among 67 hospitalized patients, 13 of whom died. In addition, these investigators reported less anticoagulant effectiveness and greater fluctuations in anticoagulant control among patients given barbiturates and warfarin concurrently than in those receiving warfarin alone.

During the induction phase of anticoagulation, the simultaneous administration of a barbiturate and a coumarin drug is relatively inconsequential because coumarin doses are adjusted every 1 to 3 days for 2 to 3 weeks on the basis of repeated prothrombin test results. During this exploratory period, warfarin doses may range between 2 and 20 mg/day for individual patients before a safe and effective maintenance dose is established. In the process, barbiturate inhibition of anticoagulant therapy is offset by increased doses of warfarin necessary to achieve the desired anticoagulant results.

The serious hazard associated with the barbiturate-coumarin interaction occurs at a strategic time, 1 week or more after combined therapy when the barbiturate and frequent prothrombin tests are discontinued. This occurs most often when a patient is discharged from the hospital receiving continued anticoagulant therapy after an acute thromboembolic illness. Shortly thereafter, a high maintenance coumarin dosage often proves excessive without barbiturate inhibition and may provoke a hemorrhagic complication before marked hypoprothrombinemia is appreciated.

In a 1964 survey of university hospital records,[2] 40 of 52 patients (77 percent) with acute myocardial infarction were given coumarin and a barbiturate concurrently. In a similar survey conducted in 1974, I found concurrent coumarin and barbiturate therapy in 31 percent of 100 patients with thromboembolic diseases treated by interns and residents at the Orange County Medical Center, and in 44 percent of 100 similar patients treated by private physicians in four neighboring hospitals. Although some educational progress has been made, it is evident that many physicians are unaware of or choose to disregard the barbiturate-coumarin interaction and its potentially dangerous consequences. Because therapeutic alternatives are available, barbiturates should not be administered to patients receiving oral anticoagulant therapy.

Glutethimide

Shortly after the discovery of barbiturate inhibition of coumarin activity, Grilli[1] administered glutethimide as an alternative sedative for several weeks to 25 patients receiving ethyl biscoumacetate and observed no interference with anticoagulant therapy. This is surprising because subsequent investigators have reported glutethimide inhibition of coumarin activity[14] and acceleration of coumarin metabolism by enzyme induction in man[11,12,14] and animals.[13] The speed of onset, magnitude and duration of action of coumarin inhibition by glutethimide approximates that of phenobarbital; therefore the clinical implications for both sedatives are the same.

Chloral Hydrate

Several investigations of the pharmacology and clinical significance of chloral hydrate interference with coumarin therapy have yielded conflicting results.[14–19] Most of the evidence suggests that chloral hydrate accelerates warfarin metabolism by displac-

ing it from serum proteins, making available more free warfarin at hepatic receptor sites to block vitamin K activity and at hepatic catabolic sites for rapid biotransformation. Warfarin displacement from serum albumin has been demonstrated in vitro, and warfarin potentiation and accelerated metabolism in vivo, by trichloracetic acid, a highly acidic metabolite of chloral hydrate which accumulates in the serum.[16,17] Chloral hydrate potentiates anticoagulant activity only transiently, however, and to a very limited extent.[23] The present studies, plus those of Breckenridge[18] and Griner[19] and their associates, indicate that the intensity of the chloral hydrate-coumarin interaction is not sufficient to be significant clinically. Chloral hydrate may be given safely to patients receiving oral anticoagulant therapy without additional caution in prothrombin test monitoring.

Methaqualone

A mild inhibition of anticoagulation was noted during and shortly after the administration of methaqualone in the present study. Although this trend was not statistically significant, there is reason to believe that it did not occur by chance. Methaqualone has been shown to induce hepatic microsomal enzyme synthesis in the rat[24] and to increase urinary excretion of D-glucaric acid in man,[25] an indirect determinant of liver microsomal enzyme induction.[26] However, according to Smyth,[21] phenobarbital is a far more potent and less specific hepatic enzyme inducer than methaqualone. He observed that young rats pretreated with the former sedative had a fivefold greater increase in these enzymes than in those treated with the latter drug. These findings suggest that methaqualone interacts metabolically with coumarin drugs, but the impact is too small to be clinically significant. This observation is not unique in the clinical pharmacology of the oral anticoagulant drugs. Other commonly used sedatives, chloral hydrate[16,17] and meprobamate,[27,28] interact with the coumarin drugs pharmacologically, but the clinical results are insignificant.

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Hemophilus Aphrophilus Endocarditis: Review of 23 Cases

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A case of bacterial endocarditis caused by Hemophilus aphrophilus is described, and 22 previously reported cases are reviewed. Eleven patients died and 12 survived; comparison of these two groups reveals that the patients who died were in the older population. The male/female ratio was 3.6:1. The organism was difficult to identify but had a wide range of in vitro bacteriologic sensitivities. This type of endocarditis is frequently associated with emboli and congestive heart failure; each occurred in 9 of 11 fatal cases and 3 of 12 nonfatal cases. Among the nonfatal cases, two patients had both emboli and congestive heart failure, requiring aortic valve replacement despite their precarious clinical condition. Initial drug therapy before results of antibiotic sensitivity tests are known should consist of penicillin combined with streptomycin. When emboli or congestive heart failure appears in Hemophilus aphrophilus endocarditis, early surgical intervention with valve replacement is indicated.

Endocarditis due to Hemophilus aphrophilus is rare. Since Khairat's original description[1] in 1940, an additional 41 cases have been reported.[2–20] Because of the infrequency of this type of endocarditis, the difficulties in identifying the organism in the microbiologic laboratory and the high mortality rate, we report another case and summarize the literature.

Recently, cardiac valve replacement has provided an additional means of salvaging patients in potentially fatal cases of endocarditis. In the case reported here and in one previous instance,[18] aortic valve replacement during the period of active infective endocarditis due to Hemophilus aphrophilus resulted in survival.

Case Report

A 40 year old white man was transferred to The Mount Sinai Hospital on March 30, 1971 because of recurrent persistent high fever, the development of a new heart murmur and increasing congestive heart failure.

Three weeks before admission, the patient underwent 7 days of treatment with tetracycline and aspirin for shaking chills and fever (temperature to 103° F) of 1 week's duration. Results of physical examination, blood count and chest roentgenogram at the onset of the illness were reported to be normal. Within 1 week the fever abated, only to recur 1 week later. There was no history of rheumatic fever, preexisting heart disease or heart murmur.

Examination on admission to another hospital on March 25, 1971 revealed an acutely ill man with toxic appearance and tachypnea (26/min) at rest. Blood pressure was 100/50 mm Hg; the pulse was regular and slightly bounding with a rate of 110/min. A small petechia was present on the right lower eyelid, and there were a few splinter hemorrhages in the nail beds of the right hand. Bibasilar rales were audible. The maximal apical impulse was in the fifth intercostal space at the midaxillary line. A harsh, grade 2-3/6 systolic ejection murmur, heard best at the base, radiated to the neck. A grade 2/6 early diastolic blowing murmur was heard along the left sternal border and over the aortic area.

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Clinical course: Administration of ampicillin, which had been started on admission, was discontinued and multiple blood cultures were taken during the next 72 hours. Thereafter, the patient was given: streptomycin, 2 g intramuscularly every 12 hours; aqueous penicillin, 40 million units/day intravenously; and oxacillin, 1 g intravenously every 4 hours. Four days after admission, the left leg was cool to the touch and no pulse was felt below the femoral artery. Because of this complication, the continued fever and increasing congestive heart failure, the patient was transferred to The Mount Sinai Hospital on March 30, 1971.

Examination upon transfer disclosed findings similar to those previously noted, except that the aortic diastolic murmur had increased to grade 3/6 intensity, basilar rales were more prominent and hepatomegaly had developed. The temperature was 102° F.

Laboratory data revealed a hemoglobin value of 10.6 g/100 ml and hematocrit of 32 percent. White blood cell count was 21,700/mm^3 with 66 percent neutrophils, 24 percent band forms, 8 percent lymphocytes and 1 percent monocytes. Reticulocyte count was 4 percent. Blood urea nitrogen was 17 mg/100 ml, glucose 140 mg/100 ml, chlorides 92 mEq/liter, carbon dioxide 27 mEq/liter, potassium 4.3 mEq/liter and sodium 134 mEq/liter. Total serum bilirubin was 1.9 mg/100 ml, alkaline phosphatase 165 international units (IU)/ml, lactic dehydrogenase 30 IU/ml and glutamic oxaloacetic transaminase 90 IU/ml. Urine analysis revealed a specific gravity of 1.022, proteinuria (3+) and a rare red and white blood cell per high power field. Chest X-ray examination revealed prominent pulmonary vasculature bilaterally and fluffy alveolar infiltrates suggestive of pulmonary edema. There were small bilateral pleural effusions (Fig. 1). The electrocardiogram revealed sinus tachycardia (107/min), slight S-T depressions and diphasic or inverted T waves in leads I, II, aVL and V_2 to V_6 (Fig. 2A).

Blood cultures from the transferring hospital revealed gram-negative rods sensitive to penicillin, ampicillin, chloramphenicol, erythromycin, streptomycin, tetracycline, gentamicin and carbenicillin. Subsequent blood cultures at Mount Sinai were sterile.

The clinical impression was bacterial endocarditis leading to acute aortic insufficiency and pulmonary edema. In accordance with the sensitivity studies, the patient was given carbenicillin, 5 g intravenously every 4 hours, and colistin, 100 mg intramuscularly every 8 hours. Treatment with digitalis and diuretic agents was continued. The embolic process to the left lower limb subsided without specific therapy, but the patient's condition continued to deteriorate; body temperature was 101.8°; and he had increasing congestive failure despite an intensive medical regimen.

Surgical findings and procedure: On April 2, 1971 the patient underwent aortic valve replacement. While he was under endotracheal anesthesia, the heart was exposed through a median sternotomy, and the pericardium was opened widely. Because of the unstable condition of the patient, cardiopulmonary bypass was performed in standard fashion as expeditiously as possible using dual caval cannulation with return of the perfusate by way of the right femoral artery. A Temptrol® (Bentley Laboratories, Inc.) oxygenator was used. Perfusion was carried out under normothermic conditions employing 50 percent hemodilution. Both coronary arteries were perfused.

The left ventricle was minimally enlarged, and the other chambers appeared normal. The aortic valve was destroyed; there was major perforation of the right coronary

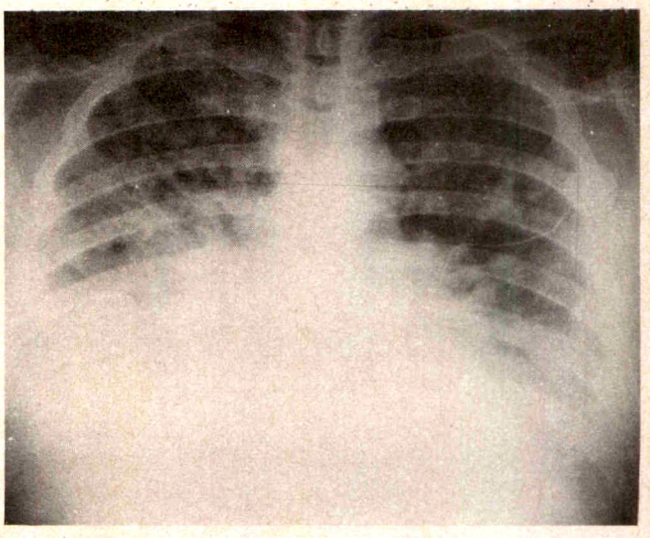

FIGURE 1. Preoperative chest roentgenogram (April 2, 1971).

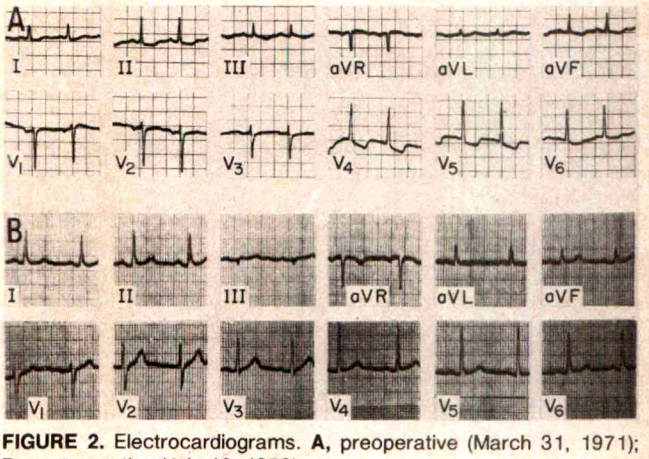

FIGURE 2. Electrocardiograms. **A,** preoperative (March 31, 1971); **B,** postoperative (July 12, 1973).

leaflet as well as fragmentation of the left coronary leaflet, sparing the noncoronary cusp. The infection had penetrated through the base of the aortic root into the myocardium. Large granular friable excrescences were attached to the peripheral portions of the aortic leaflets. After excision of the necrotic aortic valve and debridement of the annulus, a 21 mm Bjork-Shiley tilting disc prosthesis (Shiley Laboratories, Inc.) was implanted. Deep circumferential sutures were positioned in the region of the aortic root. At the conclusion of the procedure, cardiac performance was adequate at low levels of ventricular filling pressure. The patient tolerated the procedure well.

Postoperative course: Six days after admission and 4 days postoperatively, Hemophilus aphrophilus was identified as the organism grown from the blood culture before institution of antibiotic therapy. The results of sensitivity tests were identical to the previous findings. Administration of carbenicillin was discontinued, and aqueous penicillin, 6 million units every 4 hours, was instituted and given intravenously for 3 weeks. Anticoagulation was begun on the 4th postoperative day, and the postoperative course was essentially uncomplicated. The fever abated and the heart size diminished (Fig. 3A). The patient was discharged on May 7, 1971.

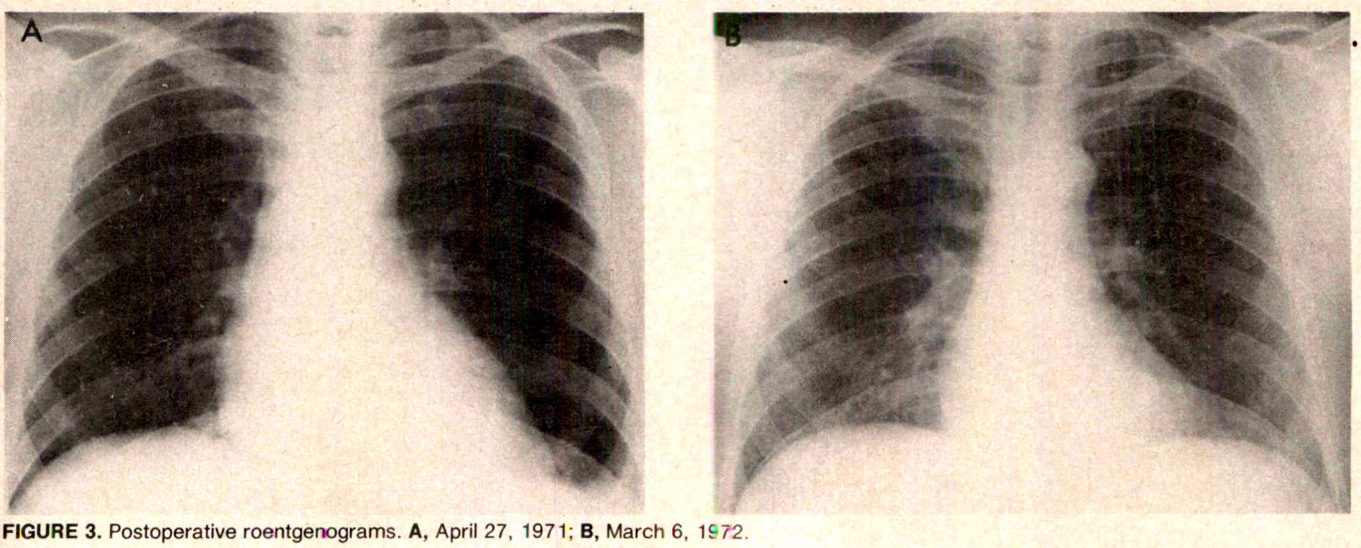

FIGURE 3. Postoperative roentgenograms. **A,** April 27, 1971; **B,** March 6, 1972.

In August 1971, the patient had homologous serum hepatitis from which he recovered uneventfully. In March 1972 he underwent elective inguinal hernioplasty, and in December 1972 a cholecystectomy; both procedures were successful. He has returned to full-time employment, is maintained on anticoagulant therapy and has a normal heart size (Fig. 3B). A short systolic murmur is heard over the base of the heart, and an electrocardiogram taken on July 12, 1973 was normal except for a diphasic T wave in lead aVL (Fig. 2B).

Microbiology: The organism, originally isolated at the transferring hospital, was characterized as Hemophilus aphrophilus at The Mount Sinai Hospital by the Diagnostic Microbiology Division.

Smears revealed the presence of small gram-negative coccobacillary forms. The organism was plated on sheep blood, chocolate and mannite agar. No growth occurred on MacConkey or Endo agar. The organism fermented maltose, glucose, sucrose and lactose but failed to ferment xylose or mannitol. The catalase, urease and indole reactions were negative. Positive reactions were elicited for oxidase and nitrate reduction.

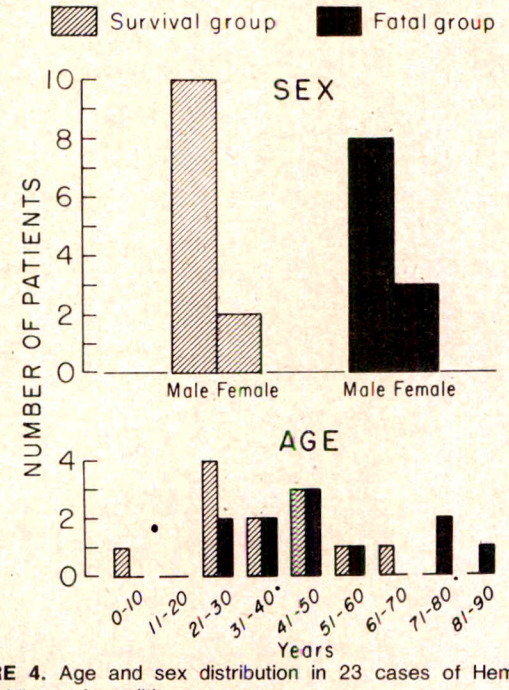

FIGURE 4. Age and sex distribution in 23 cases of Hemophilus aphrophilus endocarditis.

Review of the Literature

Twenty-two published case reports of Hemophilus aphrophilus endocarditis contained sufficient data for analysis[1–18] and, combined with our case report, comprise a total of 23 cases. Twelve patients survived and 11 died from the disease. The age and sex distributions are shown in Figure 4; male patients predominated in both groups; the overall male/female ratio was 18:5. The mean age of the survivors was 37 years and of the nonsurvivors, 50 years. The patients' sex did not affect the mean age of the group (female patients 45 years; male patients 43 years). However, the female patients who survived were younger (mean age 19 years) than the female patients who died (mean age 63 years). The male patients who survived had a mean age of 41 years; those who died had a mean age of 45 years.

Clinical features: The portal of entry could be elicited in 11 cases: the teeth in 5, upper respiratory tract in 4, and skin and prostate gland in 1 each. Only 1 of the 11 patients who died received antibiotic treatment before hospital admission, whereas 7 of the 12 who survived had been so treated. The interval between the onset of symptoms and hospitalization was not significantly different in the two groups (Fig. 5). Of the 12 patients who survived, 8 had rheumatic heart disease and 4 had no preexisting heart disease. Among the 11 who died, 2 had no previous heart disease, 7 had rheumatic heart disease, 1 had arteriosclerotic disease and 1 had heart disease of unknown origin. The most striking clinical difference between the two groups related to the incidence of systemic emboli and congestive heart failure (Fig. 6). In the 11 fatal cases, 7 patients had both emboli and congestive heart failure, and 2 each had emboli or congestive

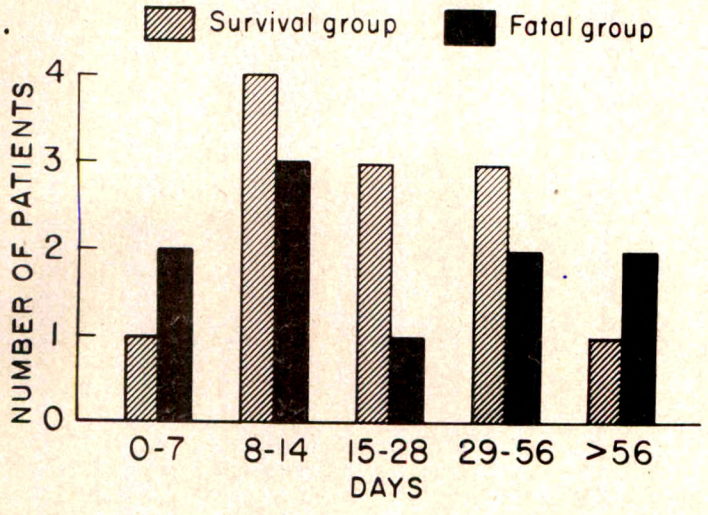

FIGURE 5 (above). Onset of symptoms in nonfatal vs. fatal cases before hospital admission.

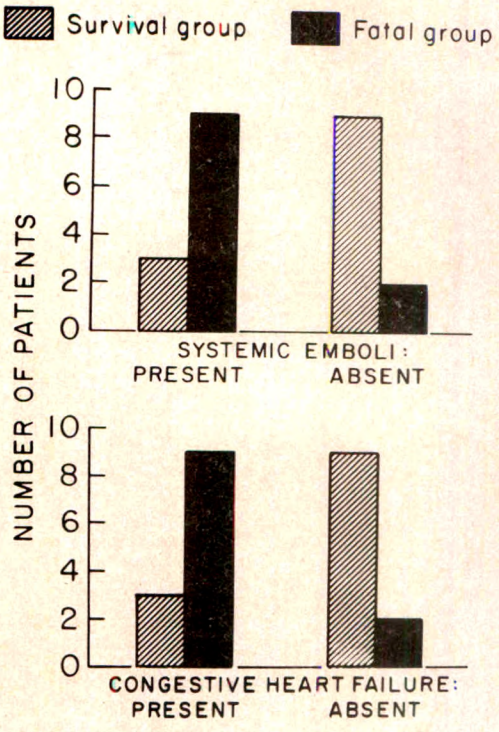

FIGURE 6 (right). Incidence of systemic embolism and congestive heart failure in fatal and nonfatal cases.

TABLE I

Distribution of Systemic Emboli in Cases of Hemophilus Aphrophilus Endocarditis*

Case no.	Site of Embolus
	Fatal Cases
1	Saddle embolus to aorta; spleen; kidney
2	Spleen
3	Brain; abdominal aorta
4	Brain
5	Brain
6	Spleen; myocardium; brain
7	Coronary artery; spleen
8	Kidney; left common iliac artery
9	Right femoral artery; mesenteric artery
	Nonfatal Cases
1	Brain; kidney
2	Right popliteal artery; left femoral artery
3	Left femoral artery

* Cases as in Table III.

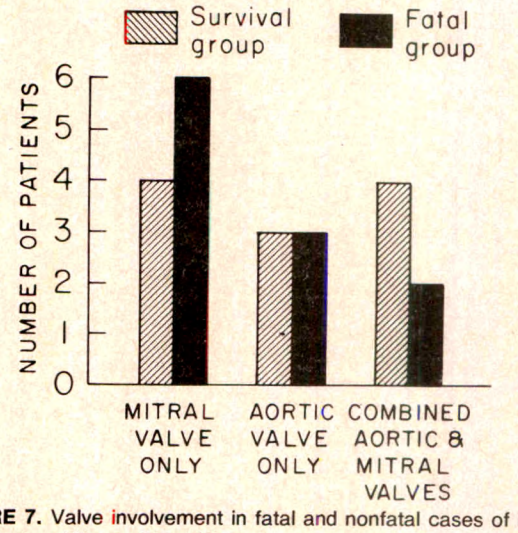

FIGURE 7. Valve involvement in fatal and nonfatal cases of Hemophilus aphrophilus endocarditis.

heart failure alone. In the 12 nonfatal cases, 3 patients had both systemic emboli and congestive heart failure. One of these patients recovered with conventional drug treatment, including antibiotic and anticoagulant therapy. However, the clinical state of two of this group deteriorated rapidly, and both had emboli, congestive heart failure secondary to aortic insufficiency and persistent activity of the bacterial endocarditis. Emergency surgical replacement of the aortic valve was performed with salutary response and recovery in both. The patients in the other nine nonfatal cases had neither emboli nor congestive heart failure.

Systemic emboli, when present, were multiple in six of nine fatal cases and two of three nonfatal cases (Table I). Five patients had emboli to the brain and six had emboli to the abdominal aorta or arteries of the lower limb. Surgical embolectomy was necessary in only one patient, who had emboli to both the right popliteal and left femoral arteries. It was not necessary to intervene surgically in the remaining patients with peripheral emboli.

The mitral valve was involved more frequently than the aortic valve (Fig. 7), but no differences between the fatal and nonfatal cases could be discerned. Two patients with aortic valve endocarditis

TABLE II

Results of Antibiotic Sensitivity Tests in 23 Reported Cases of Hemophilus Aphrophilus Endocarditis

	Sensitive	Resistant	Not Tested
Penicillin	10	3	10
Streptomycin	10	0	13
Chloramphenicol	7	0	16
Tetracycline and derivatives	9	0	14
Ampicillin	6	0	17
Kanamycin	5	0	18
Cephalosporin	3	0	20
Erythromycin	2	1	20
Gentamicin	1	0	22
Colistin	1	0	22
Vancomycin	0	2	21
Neomycin	0	1	22
Bacitracin	0	1	22
Methicillin	0	1	22
Oxacillin	0	2	21

had aneurysms of the sinus of Valsalva and both died. Two of the surviving patients with aortic valve endocarditis underwent successful valve replacement during the acute stage of the infection.

Hemophilus aphrophilus was identified in the blood of all 23 patients. The interval from admission to positive identification was recorded in 18 cases (Fig. 8). In 7 of 11 patients who survived and in 3 of 7 who died, the organism was identified within 1 week; in the remaining patients, identification was delayed.

In vitro sensitivity to antibiotic agents was reported in only 13 cases (Table II), and it is not possible to draw conclusions from this small group. Further, the antibiotic regimens employed (Table III) were so disparate that one cannot assess the most efficacious treatment of this disease. In the 12 nonfatal cases, 3 patients received penicillin and streptomycin alone, 2 each received penicillin or streptomycin plus an added antibiotic agent and 7 (including 2 requiring surgery) initially received penicillin and streptomycin but were then given other drugs. In the 11 fatal cases, 4 patients were given penicillin alone or in combination with streptomycin, 2 were given penicillin with antibiotic agents other than streptomycin, 2 were initially treated with penicillin but then given other antibiotic agents and 3 were never given penicillin.

Anemia was noted in 7 of 11 patients who survived and in 8 of 9 patients who died. All of those who died had leukocytosis, whereas six survivors had a normal white blood cell count.

Necropsy, performed in eight cases (Table IV), revealed mitral valve disease in six cases, five with persistently active infection and evidence of both congestive heart failure and emboli. Of the two patients with aortic valve disease, one had persistent infection, emboli and congestive heart failure and the other died of rupture of the aortic valve secondary to the bacterial endocarditis although evidence of infection had disappeared.

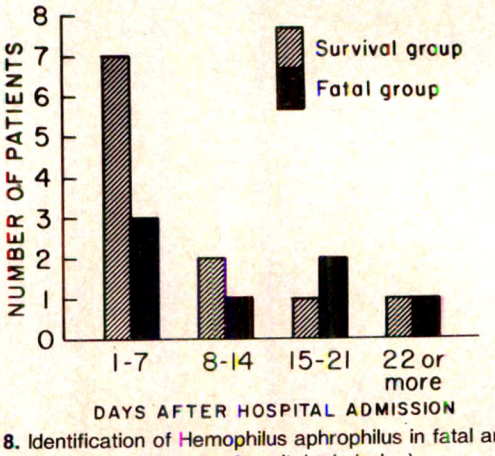

FIGURE 8. Identification of Hemophilus aphrophilus in fatal and nonfatal cases (number of days after hospital admission).

In an additional 15 cases reported by Page and King,[19] there are insufficient data for adequate analysis. Dahlgren and Fishbach[20] described five patients with Hemophilus aphrophilus endocarditis. There were four male patients and three with emboli, two of whom died. Despite the paucity of the information concerning these patients, the salient features of male predominance, high incidence of peripheral emboli and high mortality rate are confirmatory of the findings in the remainder of the literature.

Discussion

Bacteriology

Hemophilus aphrophilus is a small gram-negative nonmotile, nonencapsulated coccobacillus closely resembling both Actinobacillus actinomycetemcomitans and HB-I strains as well as members of the pasteurella and brucella genera.[21,22] Isolation was first described by Khairat,[1] who emphasized the dependence of the X factor (hemin). However, when King and Tatum[23] tested these strains they could not find X factor dependence. They noted that the characteristic might have been lost on subculture. Boyce et al.[24] tested the original isolates and found X factor dependence, although X-independent variables could be selected and isolated.

Carbon dioxide enhances growth of Hemophilus aphrophilus and HB-I and is necessary for isolation of Actinobacillus actinocycetemcomitans. Hemophilus aphrophilus grows in liquid medium as tiny compact granules adherent to the sides of the tube; similar observations have been made with Actinobacillus actinomycetemcomitans and HB-I strains.[21,22]

Colonial morphologic studies on blood agar usually reveal white to grey opaque colonies, about 0.5 mm in diameter at 24 hours. The optimal temperature for growth is 37° C. Microscopic examination of the colonies on mannite or blood agar reveals a centrally located stellate configuration.[21] However, this phenom-

TABLE III

Summary of Antibiotic Therapy in 23 Cases of Hemophilus Aphrophilus Endocarditis

Case no.	Author	Year of Treatment	Treatment Schedule	Temperature Response
	A. 11 Fatal Cases			
1	Khairat[1]	1940	Su	0
			followed by Sp	0
2	Toshak and Bain[2]	1954	T, A, C	0
			followed by P	+
3	Fortuine and Bell[3]	1963	P, E	0
			followed by P, Su	+
4	Sutter and Finegold[4]	1963	P, Su, T	0
			followed by P, T, K	+
5	Quinn et al.[5]	1964	P	0
			followed by A	+
6	McClung et al.[6]	1965	T	0
			followed by P	0
			followed by Ce	+
7	Sutter and Finegold[4]	1966	P, Su	0
8	Sutter and Finegold[4]	1967	P, Su, K	0
			followed by P	+
9	Farrand et al.[7]	1969	A	0
			followed by A, Ce	+
10	Pine and Ballard[8]	1970	P, C	+
11	Spicer and Mitchell[9]	1970	Ce, Su	+
	B. 12 Nonfatal Cases			
1	Witorsch and Gorden[10]	1955	P, St	+
2	Keith and Lyon[11]	1961	P, St	+
			followed by T, Co	+
3	Vargas et al.[12]	1961	P, St	+
4	Wittorsch and Gordon[10]	1963	P, St	+
5	Wittorsch and Gordon[10]	1963	P, St plus C added later	+
6	Raper and Kemp[13]	1964	P, St, A	+
7	Russell[14]	1964	C	+
			followed by C, St, K	+
8	Dung and Lin[15]	1964	P, St	+
			followed by T, M	+
9	Bauer and Walker[16]	1965	P, St	0
			followed by A, St	+
10	Goldberg and Cecil[17]	1965	P, St	0
			followed by A, St, K, Pr	+
11	Gullott[18]	1970	P, St	0
			followed by A, G, surgery	+
12	Present case	1971	T	0
			followed by A	0
			followed by P, St, O	0
			followed by Ca, Co	0
			followed by P, surgery	+

A = ampicillin; C = chloramphenicol; Ca = carbenicillin; Ce = cephalothin or cephalosporin; Co = colistin; E = erythromycin; G = gentamicin; K = kanamycin; M = methicillin; O = oxacillin; P = penicillin; Pr = prednisone; Sp = sulfanilylamine pyridine; St = streptomycin; Su = sulfanilamide; T = tetracycline or derivative.

enon has also been observed with colonies of Actinobacillus actinomycetemcomitans.[22]

There are biochemical characteristics that distinguish Hemophilus aphrophilus from Actinobacillus actinomycetemcomitans and HB-I strains. Hemophilus aphrophilus is differentiated from Actinobacilus actinomycetemcomitans by ability to ferment lactose and sucrose and failure to ferment xylose. Both are differentiated from HB-I strains, which do not ferment either glucose or maltose and have different colonial morphologic features.

Antibiotic sensitivity: Using the modified two-tube dilution test,[25] the organism in our patient was found sensitive to these antibiotic agents: penicillin, ampicillin, chloramphenicol, erythromycin, streptomycin, tetracycline, gentamicin and carbenicillin. Page and King[19] tested 40 strains by the tube dilution test and found all to be sensitive to streptomy-

TABLE IV

Postmortem Findings in Eight Fatal Cases of Hemophilus Aphrophilus Endocarditis

Case no.	Valve	Emboli	CHF	Active BE
1	M	+	+	+
2	A, An	+	+	+
4	M	0	0	0†
5	A	0	+	0
7	M	+	+	+
8	M	+	+	+
9	M	+	+	+
10	M	+	+	+

* See Table III B for authors and reference.

† Acute focal aortitis.

A = aortic valve; An = aneurysm of sinus of Valsalva; BE = bacterial endocarditis; CHF = congestive heart failure; M = mitral valve.

cin, tetracycline and chloramphenicol. Values for sensitivity to ampicillin and penicillin ranged from 35 to 48 percent, respectively, among the isolates tested. Sutter and Finegold[4] tested 14 strains by plate dilution tests and found that all strains were susceptible to penicillin (0.8 μg/ml), streptomycin (6.1 μg/ml), gentamicin (0.8 μg/ml), chloramphenicol (0.8 μg/ml) and rifampicin (0.8 μg/ml). Twelve of 14 (86 percent) strains of Hemophilus aphrophilus were sensitive to 6.25 μg/ml or less of ampicillin. Hemophilus aphrophilus strains were resistant to vancomycin, lincomycin and bacitracin. Recently Kraut et al.[26] incorporated bacitracin in media to select for Hemophilus aphrophilus strains in specimens from the oral cavity of normal adults and conclusively demonstrated their presence in 33 percent of those examined.

An interesting finding in Hemophilus aphrophilus endocarditis is the preponderance of male subjects infected (78 percent). The overall sex ratio of bacterial endocarditis is approximately equal.[27,28] However, there is a definite male preponderance in patients over 50 years of age, with male/female ratios 2:1 to 5:1 in the reports reviewed by Weinstein and Rubin.[29] These authors also noted that female patients predominate in the group less than 35 years of age (60 percent of cases). The greater prevalence of male patients in our series cannot be accounted for on the basis of age, nor is there any demonstrable sex-linked factor known concerning the portal of entry of the organism.

Indications for Early Cardiac Surgery

Active and uncontrolled bacterial endocarditis remains a therapeutic challenge. Although the introduction of antibiotic agents has dramatically reduced the immediate mortality rate in patients with infective endocarditis,[30] a significant number of patients subsequently die from cardiac failure secondary to severe valvular damage.[31] Heart failure occurred in 48 percent of 148 cases reviewed by Vogler et al.,[32] and the mortality rate in this group of patients was 63 percent. In the present series, congestive heart failure developed in 12 of 23 patients, 9 of whom died.

Congestive heart failure: One of the most critical indications for surgical intervention in cases of infective endocarditis is the development of intractable congestive heart failure due to disruption of valve leaflets or their supporting structures. At times, medical management alone may result in a salutary response, but in the case reported here and that of Gullot[18] surgical replacement of the aortic valve was necessary as a life-saving measure. Intractable congestive heart failure has been reported as the most common cause of fatality in infective endocarditis.[33] Aortic valve involvement is most often the cause of this problem,[34–36] but severe mitral insufficiency has also required prompt surgical replacement of the valve.[37,38] Thus, persistent infection on the affected valve is not a contraindication to cardiac surgery when cardiac insufficiency cannot be managed medically.[33]

Aneurysm of sinus of Valsalva: Another important indication for early cardiac surgery in patients with endocarditis is the development of an aneurysm of the sinus of Valsalva. Acute cardiac failure, grossly elevated jugular venous pressure, increasing hepatomegaly and a continuous basal murmur should signal the development of this complication. Immediate surgical intervention is necessary.[33] Two of the 11 nonsurvivors of Hemophilus aphrophilus endocarditis had an acquired aneurysm of the sinus of Valsalva.[2,5]

Failure of response to antibiotics: When infective endocarditis does not respond to antibiotic agents administered in demonstrated bactericidal levels or is caused by organisms without known effective bactericidal agents, surgical removal of the infected valve must be considered.[33,39–44] This is particularly true of fungal endocarditis. Our case of Hemophilus aphrophilus endocarditis demonstrated failure of response to antibiotic agents with proved in vitro bactericidal effectiveness until the aortic valve was surgically removed.

Systemic embolism: This is a frequent complication of infective endocarditis. Cherubin and Neu[27] reported the rate of clinical embolism at 25 percent. In their series, the frequency of emboli varied according to the infecting organism: fungi (60 percent), Staphylococcus aureus (58 percent), Neisseria and gram-negative rods (35 percent), Streptococcus viridans and Staphylococcus epidermidis (25 percent) and enterococci (15 percent). In the review by Weinstein and Rubin,[29] the reported incidence ranged from 15 to 30 percent, whereas in a study of 45 patients with endocarditis,[45] emboli were discovered in 75 percent at necropsy.[45] In our series, clinically demonstrable systemic emboli were found in 12 patients (52 percent), including 9 of the 11 patients who

died (82 percent). Recurrent mycotic embolism is now accepted as an indication for surgery.[46,47]

Hemophilus aphrophilus endocarditis has a high incidence of heart failure and systemic embolism, both of which are associated with a high mortality rate despite the use of bactericidal drugs. The presence of either of these complications necessitates consideration of early surgical intervention.

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SPECIAL ARTICLE

Cardiovascular Investigations and Fuzzy Sets Theory

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Examining the circumstances that often lead modern, mechanistic cardiovascular research into areas devoid of practical significance, we suggest that our approaches, instead of our technology, are inadequate. A method for processing information, built on the concept of "fuzzy sets," is described as a potential way out of this dilemma. This system deserves application to clinical problems, perhaps together with more classic quantitative methods, because of its practical consequences and the conceptual revitalization it may bring.

"That only is science which deals with (the) measurable . . ."

This aphorism of Yves Le Dantec has had greater impact on modern approaches to biological problems and on medical diagnosis (particularly of cardiovascular disease) than any other scientific statement in modern times. It has become virtually an article of faith accepted without question and widely used as a major criterion for assessment of scientific quality.

Hoping to leave behind a tainted history of qualitative measurement and of empiricism, and mesmerized by the success that quantitative measurement has bestowed on the so-called exact sciences, cardiologists have forced themselves to apply to their own thinking the rigorous rules of numerical analysis. They have thought they could not rest until they had defined, recorded and measured with the highest conceivable precision the various parameters that describe the cardiovascular system, including all its physiologic and pathologic variations. This methodologic asceticism seemed responsible for the recent acceleration of progress in modern hemodynamics and circulatory pathophysiology, and it appeared that a sufficient number of variables, properly recorded, would be bound to reveal all that one might wish to know about these complex systems.

Unfortunately, the considerable success afforded by expanding quantitative techniques may lead to a strictly mechanistic approach to cardiovascular physiology and cardiology. The number-crunching capacity of modern computers tends to reinforce this mystic belief in a physiologist's El Dorado filled with marvelous instruments capable of measuring and even controlling biological data sources (sometimes known as human beings) with enough precision to satisfy even a Swiss watchmaker. The same urges, rooted in the fashion of our times, contribute to a general suspicion with which nonquantitative or semiquantitative procedures (such as those employing external recording techniques) are met; such procedures do not provide "real" numbers, which have—as everyone knows—a fascinating and reassuring effect on today's basic and applied scientists.

Since so many significant problems still remain unsolved, perhaps it is not our friends the technologists but our method that has failed us. Daily reality tends to indicate that this mechanistic approach to cardiovascular phenomena is more a messianic vision than a useful method of solving the many problems that confront the working sci-

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entist and the clinician with the need for immediate, concrete decisions.

First let us note that discoveries more often raise new and perplexing riddles than they resolve old ones. Waiting for solution of these new problems, and for the picture of a system to emerge at last complete, postpones, step by step, the generation of working solutions that can effectively be used right away. Thus, at times the "ideal" solution begins to seem a mirage.

Second, the complexity of biological (especially human) phenomena is immeasurably* greater than that usually found in the inanimate world studied by those exact sciences that have been the source of our veneration for measurement. It is at best untimely to expect from biological sciences the same degree of precision that might be appropriate today for the physical sciences.

It now appears that modern quantitative measurement schemes, however sophisticated, may never be in a position to meet the presumptuous demands placed on them by the clinician or physiologist. Noordergraaf,[1] reviewing the role of computers in cardiovascular analysis, admitted that biological models quickly grow so complex that it is not possible, in the foreseeable future, to imagine computers capable of handling the data storage and processing requirements needed for adequate description of such models.

Moreover, the often dramatic communications gap between engineers and physicians adds its own difficulties, making more conspicuous the inadequacy of any strictly mechanistic, quantitative approach to relevant clinical problems. Recently, some investigators,[2,3] disheartened but still courageous after the romance between engineering and medicine of the 1960's was replaced by the realities of the 1970's, have recognized this inadequacy without going on to the conclusions it implies. Their pessimistic considerations came as no surprise to many clinicians, although one suspects they sounded a bit revolutionary to some members of official research committees.

But new trends do exist, and they were born precisely when workers became aware of the poor prospect that exact methods would solve, in concrete and effective ways, some of the issues facing basic and applied biological sciences. Design of machines capable of reproducing certain aspects of human behavior, and automation of translation and summarization, posed such problems. Recently Zadeh[4–7] proposed and began the development of a new way of approaching such questions and finding alternative solutions to problems that exact methods could not solve. His basic concept has been termed the "fuzzy set" to distinguish it from our more traditional notion of fixed sets with sharp boundaries that divide populations into clearly distinguishable classes based on the presence or absence of certain characteristics. The idea seems to be gaining rapid acceptance in the United States, and more recently in France,[8] and may offer considerable promise to clinicians as well as other investigators of highly complex and unpredictable systems.

* This word was chosen with care, for its dual meaning.

Fuzzy Sets

In ordinary Boolean algebra, the basis of our best-known logic systems, an element is either contained or not contained in a set of like items. The statement "John is a man" places him in a set that contains all men and that excludes the complementary set of non-men (Mary, his dog, a pencil, stars). Given an adequate description of the common features that describe "men," we can decide whether other existing elements are in the set or outside of it. The lines are sharp and the transition from membership to nonmembership is abrupt, and our logic systems built on these definitions demand such distinctions or the systems fail.

"Fuzzy sets," on the other hand, describe sets of elements or variables whose limits are ill-defined and imprecise; the transition between membership and nonmembership is gradual.[7] They allow "graded membership," since an element can "more or less" belong to the set—in contrast to classic mathematics in which the only possible choice for an element is to belong or not to belong to the set considered.[8] Fuzzy sets might include, for example, the set of integers "much greater" than 30, or the "very old" population, or possibly the reflux volumes associated with "major aortic insufficiency."

The concept of a fuzzy set is somewhat familiar to those who have faced methodologic deficiencies in studying complex animate systems. Although its title and definition may be new, the notion of someone being "more or less sick" is not. However, the concept does lead to a number of statements one might make about information and its processing:

1. There may be a difference in essence, or nature, between human intelligence and machine intelligence, perhaps because of the design principles the former has built into the latter. The most elegant computer still employs sequential (Boolean) logic, whereas the human brain can add to logic other *parallel and simultaneous information sources* and *thinking processes*, some of which can be partly prejudicial or authoritarian, even intuitive, in nature. Such flexibility of the animate brain, including man's, seems to result from its capacity *to filter and select* from the numerous simultaneous information sources available only those that are useful and relevant to its purpose. In other words, the human brain has many more processes available and has developed a far greater filtering capacity than has the machine.

2. Furthermore, the animate brain is perfectly capable of accepting and acting on information of a high degree of *ambiguity* and *imprecision* in contrast to the machine, which can process only adequate numerical or "hard" data. In fact, the brain is often capable of processing these imprecise and frequently biased data without seriously damaging the

overall quality of the result; Zadeh mentions, for example, that no modern computer is capable of successfully handling so trivial a human task as driving a car in rush hour traffic or parking it in a cramped space.

3. Finally, one should recognize what appears to be a *"principle of incompatibility."* The selection and integration potential of the human brain reaches a limit when, despite increasing accuracy, the amount of information concerning a complex system exceeds a certain "saturation" threshold. Beyond this point further data cannot be integrated and they lose their relevance. In such cases, precision and relevance become incompatible goals, and one can be achieved only at the expense of the other.

Summarizing, let us again examine the factors responsible for the impasse described earlier: First, the great complexity of biological phenomena of interest to us far exceeds the capacity of computers and their formal logic (developed for dealing with the inanimate world) to handle and, second, our own slavish tendency to follow the physical sciences' successful path toward precision may blind us. Still, one finds some reason to hope that the characteristics of human intelligence—selection among data sources, acceptance of imprecision and ambiguity, and a facile reprogramming capability—offer new solutions at the cost of some sense of elegance.

What forms might these alternative approaches take? The "fuzzy set" approach described leads to interesting possibilities:

1. Replacing (or adding to) precise numerical variables some *fuzzy variables,* of a certain linguistic and particularly semantic content, and generating, in addition to numerical curves, *fuzzy graphs.*[4,6,7]

2. The establishment of *fuzzy relations* between such new variables (for example, "if x is very small, then y is probably very great"). In addition to the classic notions of identity or nonidentity, we can add those of similarity or dissimilarity.[8] The advantage of these new definitions is that they encompass a wide range of real situations, frequently encountered in biological sciences, and allow us to process them with agreed-upon mathematical procedures.

3. It should be obvious by now that such heuristic notions may apply to far broader fields. We can proceed to the formulation of *fuzzy concepts, fuzzy logic* and even *fuzzy algorithms* which could be processed by (of course) *fuzzy computers!*[5,7]

Membership and Probability

These two concepts, membership and probability, involve such similar considerations that clear distinctions between them should be drawn. Probability is defined as the ratio of favorable outcomes of a given eventuality to the total possible number of outcomes, and can be clearly specified since favorable outcomes totally exclude unfavorable ones; for example, a coin toss can end only as heads or tails. The set of coin tosses includes only two subsets, one of favorable outcomes and one of unfavorable ones, mutually exclusive and sharply defined, and thus probability considerations place *on each subset of the same set* certain numerical values indicating their probability of occurrence. Membership, on the other hand, applies *to each element in the same set,* rather than to a subset, and states the degree to which the element belongs in that set. It could not be applied to a coin toss, for obviously one outcome cannot be "a little more heads" than another.

The terminology used for each helps to draw the distinction even more clearly. Probabilities must be defined in the interval 0 to 1, from no possibility to inevitable occurrence, and must also conform to certain precise axioms (called Borel-Kolmogorov axioms) which can be manipulated mathematically to derive predictions. While fuzzy set theory often makes use of the same interval, 0 to 1, to describe the value of a membership function, there are also broad verbal grading systems (none, a little, moderately, very much, enormously) or even nongraded words of high semantic impact (a "whiff" of aortic insufficiency). In other words, membership is not necessarily predictive nor precise.

In short, probability is used to define subsets within a set, each of which has sharp and distinguishable boundaries, and is *predictive* in nature. A membership function is used to indicate the degree to which an element belongs to a set with fuzzy boundaries, and is *descriptive* in nature. If one gambles on a coin toss, he will win or lose, but in describing similarities he must apply a graded scale in which the concept of membership would apply instead. The two terms are simply not equivalent.

Pattern Recognition and Data Analysis

As Kaufmann[8] elegantly demonstrated, we can determine the (fuzzy) "distance" between two fuzzy subsets, we might visualize or determine the "distance" between two graphs or patterns and we might be able to evaluate the degree of "similarity" between two curves. The degree of membership of a curve, or functional relation, observed in a given patient to sets of curves characteristic of normal or diseased function could be assessed. We might even rehabilitate and legitimize, by more rigorous processing of now rejected data sources, those external recording methods of potential usefulness to cardiology that have been heavily criticized in recent years for their inaccuracy and imprecision.

A Fuzzy View of Aortic Valvular Incompetence

As a clinical example, let us consider the classification of aortic incompetence according to the degree of volumetric regurgitation found (Fig. 1). In any patient, the degree of diastolic regurgitation through the aortic valve may theoretically take any value from 0 to V, V being the systolic ejection volume of the left ventricle. Any incompetence might be usefully defined as the degree of regurgitation expressed as

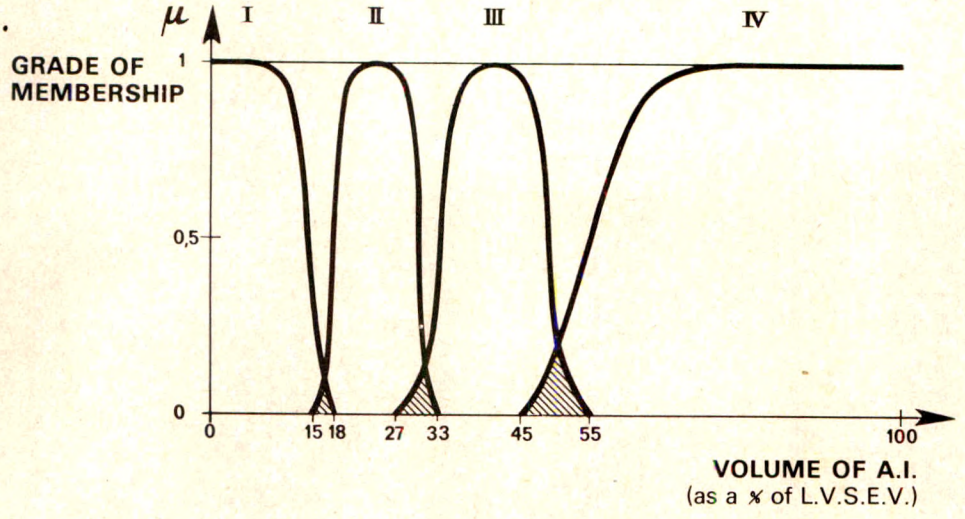

FIGURE 1. Variations of the membership function μ for the four groups of patients with aortic incompetence (A.I.)—mild, moderate, major and massive—expressed as percent of V [left ventricular ejection volume (L.V.S.E.V.)] regurgitated. As noted in the text, the values shown were chosen arbitrarily for the purpose of illustration. When $\mu = 1$, membership in a given set is certain, and when $\mu = 0$, membership in a given set is denied; for intermediate values of μ, membership is uncertain and corresponds to the hatched zones of uncertainty. The intersections of contiguous "fuzzy subsets" are shaded.

a percent (%) of V. Let us admit that we have no instrumental technique for defining, with great accuracy, regurgitation either in milliliters per beat or percent V; available techniques are indeed crude, and for obvious reasons have not been well correlated with an acceptable physical standard (for example, an electromagnetic flow transducer around the aortic root).

Yet, the common clinical practice of grading regurgitation into minor, moderate, major and massive incompetence does in fact meet our practical requirements for making prognostic or therapeutic decisions. We simply have no evidence (nor, frankly, reason to seek it) to support a contention that a more accurate, numerical or volumetric classification would significantly alter the clinician's approach to decision-making. Still, let us assume that the following (rather arbitrary) figures could be assigned to these four groups: Group I, minor incompetence, 0 to 18 percent of V; Group II, moderate incompetence, 15 to 33 percent of V; Group III, major incompetence, 27 to 55 percent of V; Group IV, massive incompetence, more than 45 percent of V. Figure 1 shows these as fuzzy sets, and within each group a number can be assigned for each possible value of the degree of incompetence: that is, a grade of membership μ. In the case of absolute and certain membership $\mu = 1$, and in the case of absolute and certain nonmembership $\mu = 0$. In addition to those values μ can take on intermediary values between 0 and 1 (since membership criteria are fuzzy) depending on whether the degree of incompetence is closer to or further from the critical (and, as noted, arbitrary) values chosen for the groups considered. The grade of membership is a function (called a *membership function,* naturally) that varies according to the familiar S-shaped curve for Groups I and IV, and according to a bell-shaped curve for Groups II and III.

The advantage of considering such groups is actually threefold: first of all, in current practice simple and widely accepted techniques are available for such grading; second, this grading system, however crude and nonquantitative it may appear, is relevant to the solution of prognostic and therapeutic problems; and third, the introduction of the fuzzy set concept in this setting allows such sets to be studied mathematically using theories and procedures now being developed.

Note in Figure 1, the intermediate zones (15 to 18 percent, 27 to 33 percent, and 45 to 55 percent), which are defined as "intersections of fuzzy subsets." At the intersection of subsets I and II, the maximal value of the membership function is about 0.1 at 16.5 percent; this does not mean that the probability of aortic insufficiency is 0.1 (which would be nonsense) for, as previously discussed, probability is not conceptually equivalent to membership. This overlap does illustrate that the two fuzzy subsets have a common part, an intersection, and that within this zone one would have to make some sort of decision; that is, there is present some ambiguity about which subset contains a particular element, and that the ambiguity is maximal for V at 16.5 percent. The same ambiguity and the same decision-making requirement exist for the other two intersections shown in the figure.

The significance of these intersections lies in the new demands they introduce. If a clinical decision rests on which fuzzy set contains a given element (that is, which class of disease does a particular patient present), the clinician must collect further information in order to "bend" his decision one way or the other until the membership function rises to a satisfactory level.

Obviously other clinical situations can be viewed in similar ways, such as problems posed by other valvular lesions, myocardial or circulatory failure, assessment of angina pectoris, and the like.

Conclusions

The classic, formal, quantitative approach to medical research and clinical decision-making now threatens us with the dangers of drowning in excessive data or of delaying our decisions until ever-more-precise

methods of measurement become available. Despite its history of success in the physical sciences, we suspect a "never-say-die" search for more and more quantitative methods applicable to biological problems is leading us toward a deadlock insofar as practical medical applications are concerned.

A new conceptual and methodologic approach deserves exploration now. Based on the concept of "fuzzy sets," it offers an alternative decision-making path that will allow us (and machines) to take into account the complex character of biological phenomena and thereby meet real clinical and experimental needs. One suspects that new and more precise sources of data, rather than new and more relevant ways of thinking about available data, will continue to attract attention, and so a certain degree of boldness—coupled with a willingness to face painful intellectual, ethical and even financial questions—may be necessary now. But when our rigorous sister science, mathematics, turns her attention away from precision and toward the real world of uncertainty, can we as physicians do less?

Acknowledgments

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Precordial Honk Due To Tricuspid Regurgitation

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A systolic honk developed in a woman with idiopathic cardiomyopathy and congestive heart failure. The honk was present only during deep inspiration, disappeared as her cardiovascular status improved, but recurred when her cardiovascular function declined. Further investigation indicated that the honk was the result of tricuspid regurgitation.

This report describes a patient with cardiomyopathy and chronic congestive heart failure in whom a systolic precordial honk developed during the course of her illness. The response of this honk to various diagnostic and therapeutic maneuvers at the bedside suggested tricuspid regurgitation and the results of cardiac catheterization confirmed the lesion. This case is the third reported instance of systolic honk secondary to tricuspid regurgitation.

Case Report

The patient is a 49 year old white woman. In January 1952, at age 27 years, she had a sore throat, cough and substernal pain that was aggravated by respiratory movements and radiated to the interscapular region. Other symptoms were dyspnea, orthopnea and pedal edema that had been present for 3 months. She had ingested large quantities of alcohol during the previous 8 years. Examination disclosed right and left ventricular hypertrophy, ventricular gallop, tender, enlarged liver and pedal edema. Electrocardiographic examination revealed premature ventricular contractions and precordial T wave inversion, suggesting anterior myocardial ischemia. On pericardial aspiration no fluid was obtained. She was treated with digitalis, diuretic agents and rest, and her condition improved. She subsequently became pregnant for the first and only time and in March 1953 was delivered of a normal infant son. Acute pulmonary edema developed immediately postpartum. After vigorous therapy the patient's condition improved and she remained relatively well for the next 13 years. However, on periodic examination she admitted to minimal dyspnea, easy fatigability and pedal edema; findings of right and left ventricular hypertrophy persisted and occasional premature ventricular contractions were noted. In 1966 she had an acute myocardial infarction manifested by typical chest pain with radiation to the left arm, sweating, dyspnea, an increase in heart size and a transient pericardial friction rub; an electrocardiogram revealed change in intraventricular conduction and transient S-T shift. In 1967 she had an episode of chest pain diagnosed as angina pectoris and associated with ventricular tachycardia. Between 1966 and 1969 the pattern of intraventricular conduction changed to left bundle branch block. Paroxysmal ventricular tachycardia recurred in 1969 and in 1970.

In January 1972 she had another acute myocardial infarction manifested by recurrent substernal pain, reduction in cardiac function with louder ventricular gallop and with distended jugular veins. Serum glutamic oxaloacetic transaminase (SGOT) was increased. A loud systolic honk was audible over the entire thorax, but was best heard along the lower substernal area where a systolic thrill was felt (Fig. 1). The patient remained at home for nearly a year on a regimen of strict bed rest, which resulted in diminution of all her cardiovascular symptoms and reduction in heart size and in intensity of the ventricular gallop; the honk gradually disappeared. In 1973 she became ambulatory, but congestive heart failure and the honk recurred. At present she

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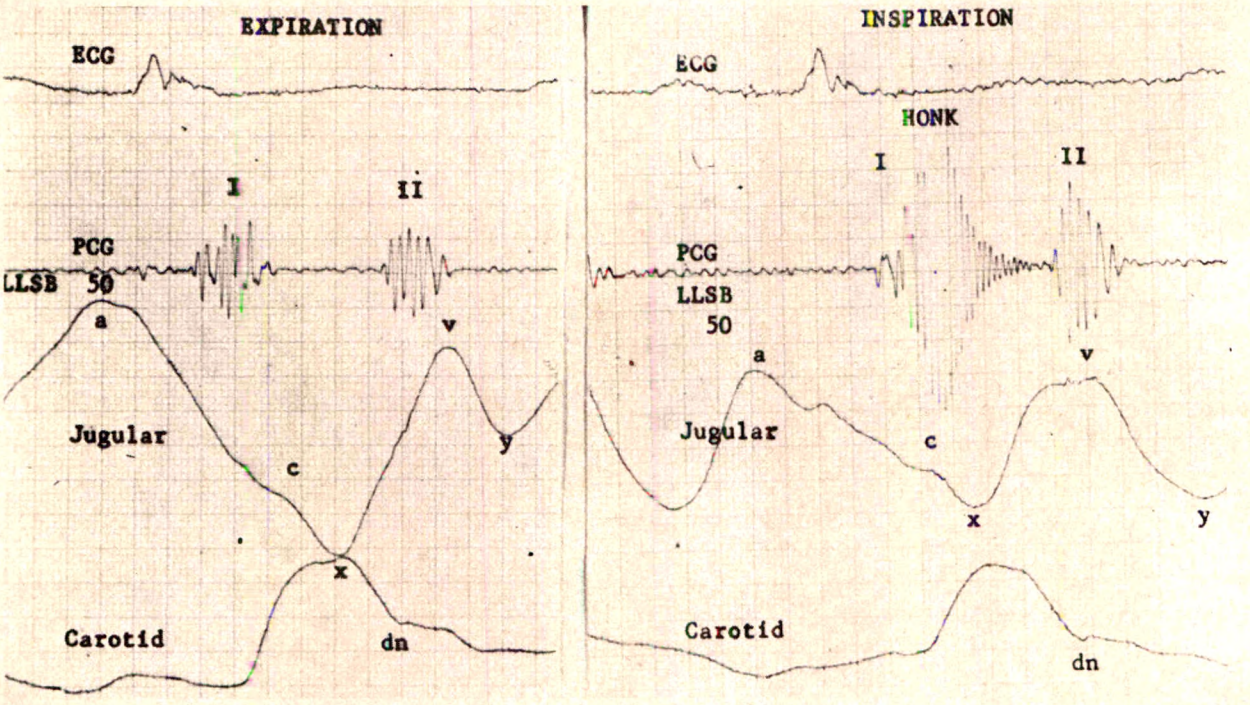

FIGURE 1. Surface phonocardiograms (PGG) recorded at lower left sternal border (LLSB) demonstrating a prominent honk, present only on inspiration. **Top tracing,** lead II of the electrocardiogram (ECG). **Bottom tracing,** left external carotid arterial pulse tracing. Right jugular phlebogram is between the phonocardiogram and carotid pulse tracing. a, c, v, x, y = waves (crests and troughs) of jugular venous pulse; dn = dicrotic notch; 50 = upper limit of sound frequency in cycles per second transmitted on phonocardiogram; I = first heart sound; II = second heart sound. Paper speed 100 mm/sec.

is fairly comfortable provided that she leads a very quiet life.

The following observations regarding the honk were made at the bedside:

1. The honk occurred only in systole and only on deep inspiration.
2. During deep inspiration, sustained for 10 to 11 seconds, the honk was loudest and lasted throughout systole during the initial 3 to 4 seconds, but became softer and occupied only the first two thirds of systole during the final 2 to 3 seconds of the sustained deep inspiration.
3. The honk became louder during deep inspiration immediately after all four limbs were elevated above the level of the heart.
4. The honk was markedly decreased in intensity but was not delayed when the patient was standing; the honk became louder when the patient squatted.
5. When the patient was supine with venous tourniquets applied to all four limbs, deep inspiration decreased the intensity of the honk but did not delay it.
6. The honk was louder with a premature ventricular contraction during deep inspiration.
7. The honk gradually decreased in intensity and disappeared after improvement in cardiovascular function.
8. The honk reappeared when cardiovascular function worsened.

At cardiac catheterization (Table I) the level of right atrial pressure was high and paradoxically rose markedly with inspiration (Kussmaul's sign), the *v* wave increasing slightly more than the *a* wave. These changes were probably the combined result of tricuspid regurgitation and decreased right ventricular compliance. The right ventricular pressures were increased because of moderately severe pulmonary arterial hypertension, which was probably caused by the marked increase in left ventricular end-diastolic pressure. There was no sign of valvular stenosis or of a shunt. The increased arteriovenous oxygen difference and the low cardiac index reflected the poorly functioning state of the ventricles. The data indicated severe cardiomyopathy with biventricular dysfunction. Coronary arteriograms

TABLE I

Cardiac Catheterization Data

Pressures (mm Hg)	
Right atrium	13 (mean at expiration)
a wave	17 (expiration)
	24 (inspiration)
v wave	13 (expiration)
	22 (inspiration)
Right ventricle	67/11
Pulmonary artery	67/34
Pulmonary artery wedge	35
Left ventricle	102/30
Aorta	102/57
Arteriovenous O_2 difference (cc/100 cc)	5.66
Cardiac output (liters/min)	2.29
Cardiac index (liters/min per m^2)	1.3
Heart rate (beats/min)	90
Stroke volume (cc)	25
Stroke index (cc/m^2)	14
Total pulmonary resistance (units)	21
Total peripheral resistance (units)	34

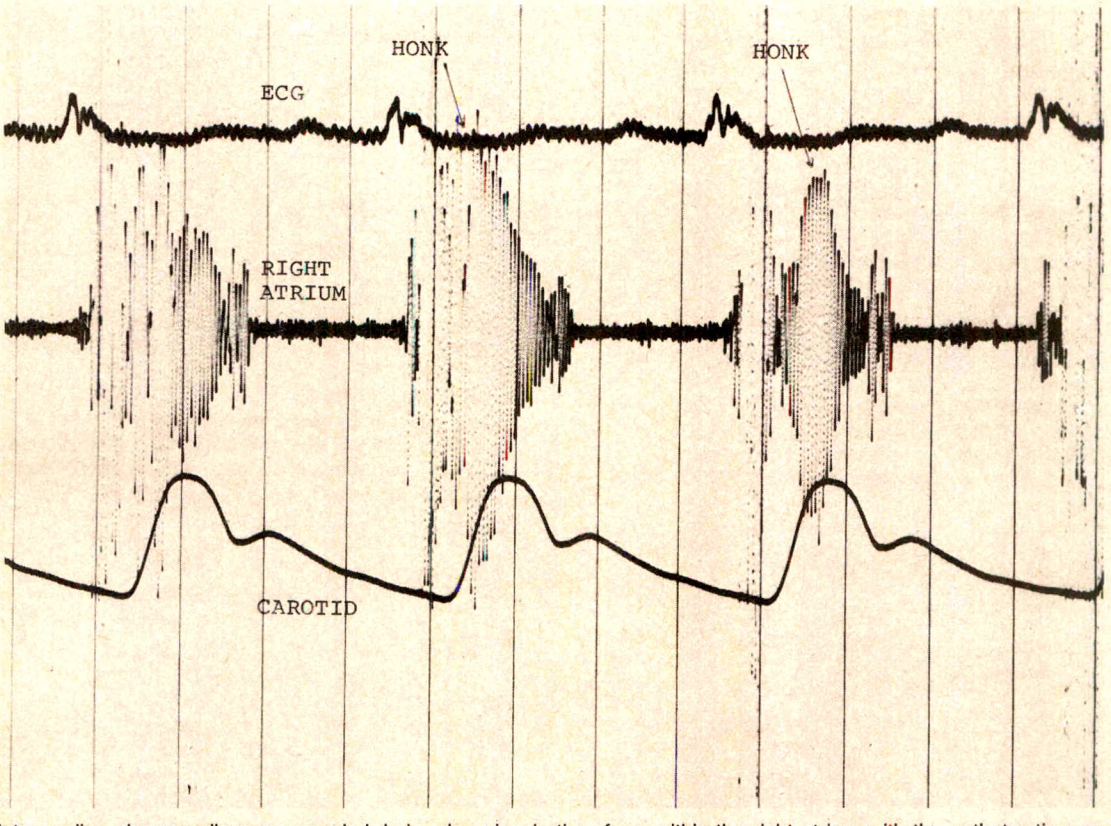

FIGURE 2. Intracardiac phonocardiogram recorded during deep inspiration, from within the right atrium with the catheter tip near the tricuspid valve. Note the prominent pansystolic honk. **Top tracing,** lead II of the electrocardiogram (ECG). **Bottom tracing,** external carotid arterial pulse tracing. Paper speed 100 mm/sec.

were normal. An intracardiac phonocardiographic catheter was pulled from the right ventricle across the tricuspid valve into the right atrium during deep inspiration. As the catheter tip entered the right atrium, the honk became extremely loud (Fig. 2). Surface and right atrial phonocardiograms recorded only a faint pansystolic murmur during expiration. Selective right ventriculography during inspiration revealed mild tricuspid regurgitation. Selective left ventriculography disclosed a dilated, poorly contracting left ventricle; there was no mitral regurgitation. Echocardiograms of the mitral valve revealed normal anterior and posterior leaflets with no evidence of valve prolapse.

Discussion

Systolic honks are loud, vibratory, sonorous murmurs of relatively pure pitch; they may be pansystolic or may occur only in early, mid or late systole.[1] Systolic honks are synonymous with the term systolic whoops; I have chosen to use the term honk because the sounds audible in this patient resemble those made by a wild goose. This peculiar murmur has been described secondary to pneumothorax.[2] However, the vast majority of patients with systolic honks have been found to have ballooning of a leaflet of the mitral valve into the left atrium during ventricular systole, usually associated with mild mitral regurgitation.[3,4] In some patients who are followed up for several years, the honk develops into a pansystolic murmur, typical of mitral regurgitation.[1] Presumably, vibrations of the mitral valve leaflets or of chordae tendineae are the source of the honk. Characteristically the honks vary in their duration, timing and intensity; they are often altered by changes in body position, state of activity or phases of respiration. Because of the danger of bacterial endocarditis, prophylaxis is advised.[1,5]

Keenan and Schwartz[6] recently described two patients with systolic honks (whoops) due to tricuspid regurgitation. The frequent association of tricuspid valve prolapse with mitral valve prolapse has recently been emphasized.[7,8] The precordial honk noted by Ainsworth et al.[8] may have been due to mitral valve prolapse. This case is the third reported instance of precordial honk due clearly to tricuspid regurgitation. The exact genesis of the murmur is unknown, but it is probably similar to those of murmurs recorded in the mitral valve area. The bedside observations suggested the development of tricuspid regurgitation associated with augmented venous return to the right heart as occurs with deep inspiration and with elevation of the limbs above the heart. The reduction and disappearance of the honk and marked improvement in cardiovascular function after prolonged bedrest[9] were probably the result of a return toward normal in the functional anatomy of the tricuspid valve.

The cause of the patient's cardiomyopathy is uncertain. She could have had viral myocarditis in 1951; it is possible that the large alcohol consumption is the basic cause of her heart disease; or disease limited

to small coronary arteries might account for her cardiomyopathy, myocardial infarctions and the finding of normal coronary arteries on coronary arteriography.[10]

Acknowledgment

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Nonobstructive Hypertrophic Cardiomyopathy Mimicking Mitral Stenosis

Documentation by Echocardiography, Phonocardiography and Intracardiac Pressure and Sound Recordings

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The physical findings in hypertrophic cardiomyopathy with left ventricular outflow tract obstruction are well described. In the absence of outflow tract obstruction the findings are less distinctive. There have been several reported cases in which the cardiac findings have suggested the diagnosis of mitral stenosis. In this report we describe a patient whose auscultatory and roentgenographic findings more closely mimicked mitral stenosis. The patient had a loud first heart sound, mitral opening snap and an apical presystolic murmur; left atrial enlargement was present. Noninvasive studies, including phonocardiography, echocardiography and apex cardiography, strongly suggested the correct diagnosis of nonobstructive hypertrophic cardiomyopathy. The diagnosis and unusual auscultatory findings were confirmed by results of cardiac catheterization and intracardiac phonocardiography. The importance of recognizing this syndrome and the use of noninvasive methods to establish the diagnosis are stressed.

Hypertrophic cardiomyopathy, or asymmetric septal hypertrophy, is a disease with a wide spectrum of clinical expression.[1,2] In the early 1960's it was recognized that hypertrophic cardiomyopathy with left ventricular outflow tract obstruction may simulate valvular aortic stenosis.[3] Since then the major focus of attention has been on the distinguishing clinical and hemodynamic differences between these two diseases. It is less well known that hypertrophic cardiomyopathy, or asymmetric septal hypertrophy, without obstruction may mimic mitral stenosis. In 1958 Teare[4] described "tumours or asymmetrical hypertrophy of the muscle and connective tissue . . . " of the heart. One of his patients with an apical mid-diastolic rumbling murmur and thrill was thought to have mitral stenosis and died after attempted valvotomy. Postmortem examination disclosed a fishmouth distortion of the mitral valve that Teare attributed to asymmetric septal hypertrophy. Recently Shabetai and Davidson[5] described three patients with asymmetric septal hypertrophy who were referred with a clinical diagnosis of mitral stenosis. Each had an apical diastolic rumbling murmur and a third heart sound gallop that had been mistaken for an opening snap. Two patients were specifically referred for mitral valvotomy. Shabetai and Davidson stressed the close clinical mimicry of mitral stenosis by asymmetric septal hypertrophy and the need for invasive hemodynamic studies to clarify the diagnosis.

In this report we describe a patient with asymmetric septal hypertrophy whose cardiac auscultatory and roentgenographic findings simulated mitral stenosis more closely than has heretofore been reported. Noninvasive methods of establishing the correct diagnosis are demonstrated, and the mitral opening snap and presystolic murmur are documented by intracardiac phonocardiography.

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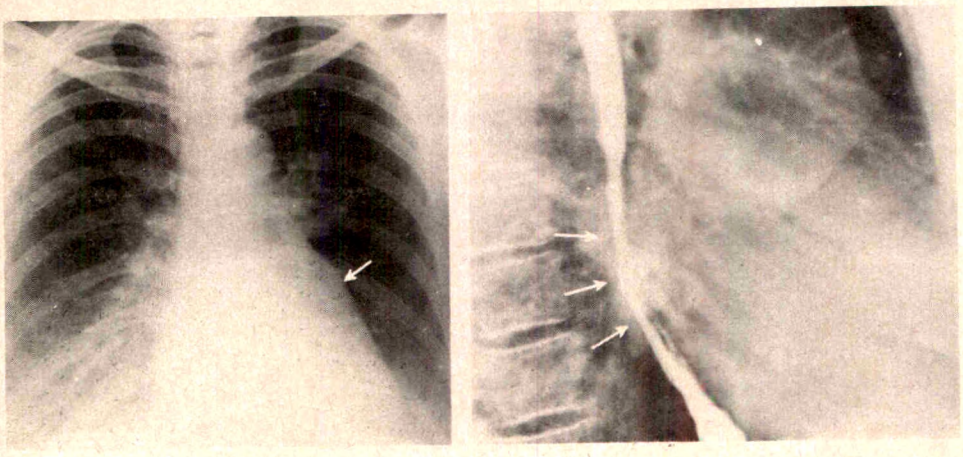

FIGURE 1. Posteroanterior chest roentgenogram **(left)** and barium esophogram **(right)** reveal borderline cardiomegaly and an enlarged left atrium **(arrows).**

Case Report

A 47 year old black woman first noted exertional dyspnea during her pregnancy in 1959 at age 33; she was told that she had a heart murmur and an enlarged heart. Her symptoms lessened in the postpartum period. She was next seen in December 1971, when she was treated for pneumonia and again told of a cardiac murmur and cardiac enlargement. She later had angina pectoris, which was precipitated by walking one block, relieved by rest, and poorly relieved by nitroglycerin. She also had exertional dyspnea and easy fatigability that progressed until she was unable to work as a domestic. Orthopnea, paroxysmal nocturnal dyspnea and ankle edema subsequently appeared. Treatment with digitalis significantly relieved her symptoms. She had no history of acute rheumatic fever or hypertension, and her family had no history of heart disease. In August 1973 she was referred to the cardiac clinic at Cincinnati General Hospital.

Physical examination revealed an overweight (170 lb) black woman with a blood pressure of 126/80 mm Hg and pulse rate of 84/min. The jugular venous pressure and jugular venous pulsations were normal as were the carotid pulses. The chest was clear to percussion and auscultation. A somewhat diffuse and sustained apical impulse was displaced 2 cm to the left of the midclavicular line in the fifth left intercostal space. The first heart sound was loud and the second heart sound was normal. A grade 3/6 decrescendo holosystolic murmur was heard at the apex and radiated to the left axilla and lower left sternal border. An early diastolic sound was heard by all examiners, but was interpreted as an opening snap by some and as a third sound gallop by others. A grade 2/6 presystolic murmur was also heard at the cardiac apex. Abdominal findings were normal. Slight pedal edema was present.

An electrocardiogram revealed left atrial enlargement without evidence of ventricular hypertrophy or other QRS abnormalities. A chest roentgenogram disclosed slight enlargement of the left ventricle and prominence of the left atrial appendage (Fig. 1). Cardiac fluoroscopy and a barium esophogram confirmed the findings of left ventricular and left atrial enlargement and revealed no intracardiac calcifications (Fig. 1).

The initial clinical diagnosis was rheumatic heart disease with dominant mitral stenosis. Subsequently, this diagnosis was excluded and the correct diagnosis of asymmetric septal hypertrophy without left ventricular outflow obstruction was strongly suggested by noninvasive studies and confirmed by invasive studies. These special studies are described later. Administration of digitalis was discontinued and the patient was given propranolol, 40 mg/day. However, her symptoms of dyspnea and fatigue increased; propranolol was discontinued and treatment with digitalis and diuretic agents was reinstituted. This drug regimen resulted in marked symptomatic improvement.

Methods

Simultaneous recordings of the electrocardiogram, phonocardiogram and indirect carotid arterial pulse were obtained with a multichannel photographic recorder and contact microphone (Hewlett-Packard). Echocardiograms were obtained using a commercially available ultrasonoscope (Smith Kline Instruments, Ekoline 20). The output of the ultrasonoscope was displayed and recorded on a multichannel (Electronics for Medicine DR8) photographic recorder. The echoes were displayed and recorded in the time-motion mode. An electrocardiogram, phonocardiogram and apex cardiogram were recorded simultaneously and in combination with the echocardiographic recordings.

Before cardiac catheterization the patient was premedicated with 50 mg of meperidine and 25 mg of promethazine administered intramuscularly. Pressures from the right atrium, right ventricle, pulmonary artery, pulmonary capillary wedge and brachial artery were recorded using a fluid-filled catheter and Statham P23Db pressure transducer. Left ventricular sound and pressure events were recorded using a Millar catheter tip micromanometer (Millar Mikro-Tip pressure transducer, model PC350) introduced percutaneously from the femoral artery. The pressure transducer was made equisensitive with the transducer recording right heart and brachial arterial pressures. All pressure and sound events were recorded on a multichannel photographic recorder (Electronics for Medicine DR8). At catheterization an echocardiogram was recorded simultaneously with the electrocardiogram and left ventricular sound and pressure events on the same multichannel recorder. With the patient at rest, pressures were recorded from the right atrium, right ventricle and the pulmonary artery and then simultaneously from the pulmonary capillary wedge and left ventricle. Simultaneous left ventricular and brachial arterial pressure recordings were obtained at rest and during an intravenous infusion of isoproterenol (4 μg/min). The Millar catheter was replaced by a Cordis (Ducor) pigtail catheter and a left ventricular cineangiogram was performed

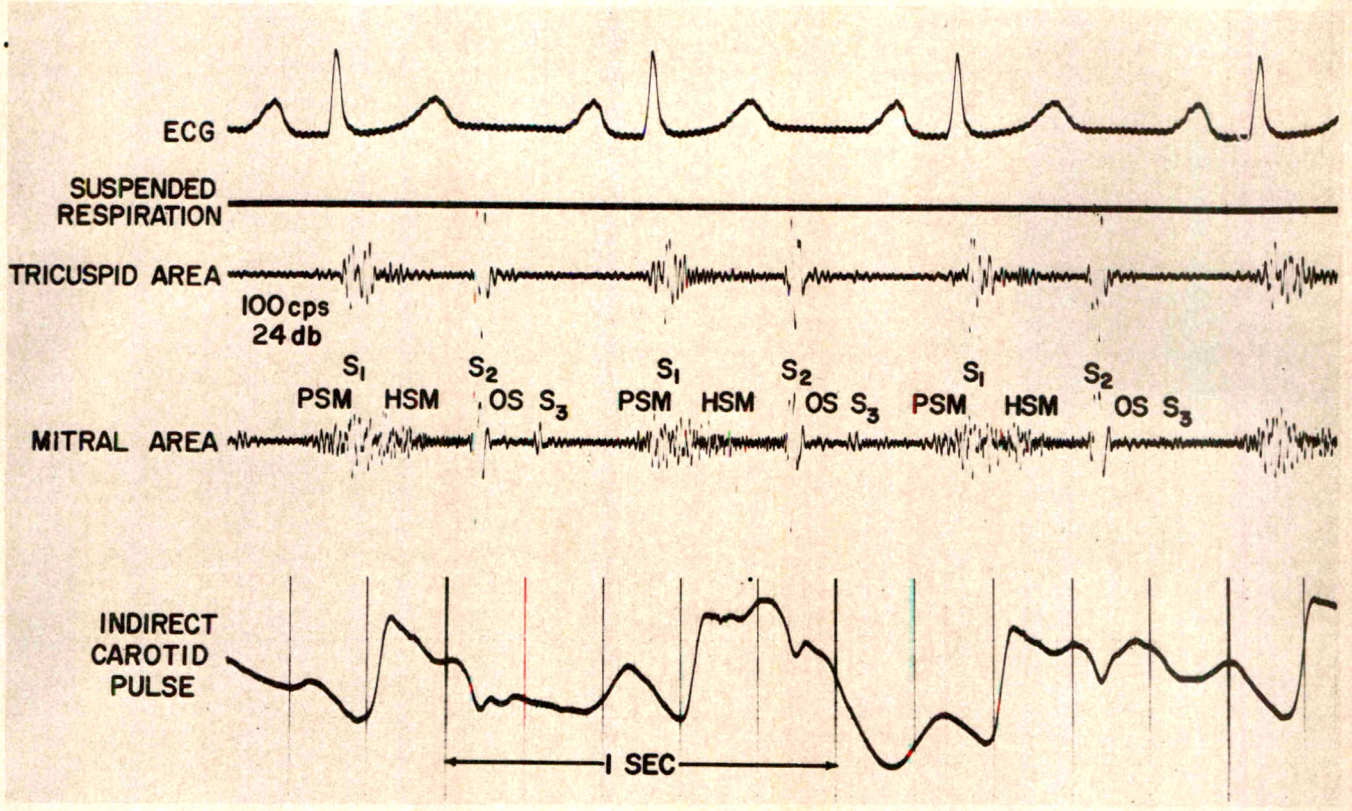

FIGURE 2. Simultaneously recorded phonocardiogram from the tricuspid and mitral areas, lead II of the electrocardiogram (ECG), respiration and an indirect carotid pulse tracing. HSM = decrescendo holosystolic murmur; OS = opening snap; PSM = presystolic murmur. See text.

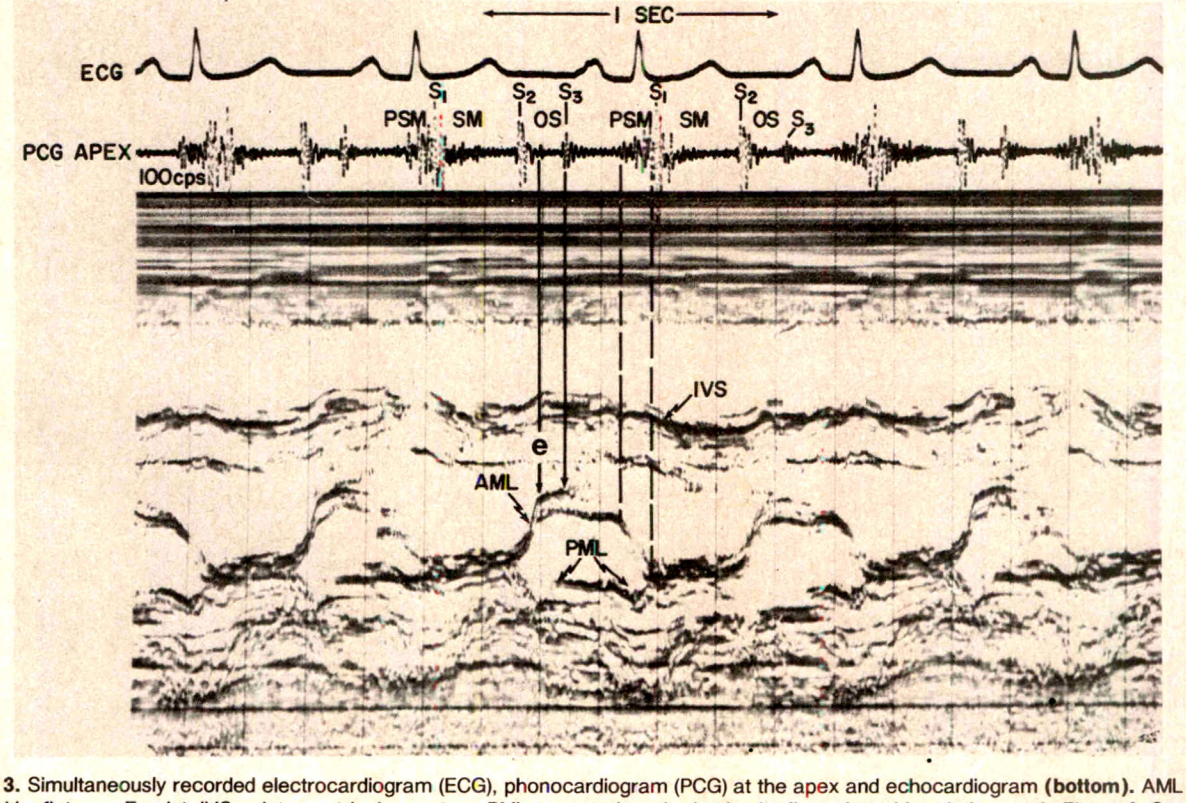

FIGURE 3. Simultaneously recorded electrocardiogram (ECG), phonocardiogram (PCG) at the apex and echocardiogram **(bottom).** AML = anterior mitral leaflet; e = E point; IVS = interventricular septum; PML = posterior mitral valve leaflet; other abbreviations as in Figure 2. See text.

with the patient in a left lateral position. Cardiac output was determined by the Fick method before administration of isoproterenol and performance of angiography.

Results

External Phonocardiographic and Echocardiographic Findings

The external phonocardiogram (Fig. 2) revealed a presystolic murmur and a loud first heart sound (S_1). A decrescendo holosystolic murmur with early accentuation extended to a normal second heart sound (S_2). There appeared to be an opening snap of small magnitude 0.10 second after S_2. In addition, a third heart sound (S_3) was recorded 0.16 second after S_2.

A simultaneously recorded external phonocardiogram and echocardiogram (Fig. 3) revealed that the opening snap coincided with the point of maximal initial diastolic opening (E point) of the anterior mitral leaflet. The anterior leaflet echo was dense and wide, suggesting thickening of the leaflet. In addition, the slope of diastolic closure was reduced to 19 mm/sec. However, the normal pattern of motion of the posterior mitral leaflet was inconsistent with the diagnosis of mitral stenosis. There was no abnormal systolic anterior motion of the mitral leaflets. The presystolic murmur occurred while the mitral valve leaflet was moving toward the closed position after atrial systole. An apex cardiogram recorded simultaneously with an apex phonocardiogram and mitral valve echogram (Fig. 4) disclosed an S_3 gallop that coincided with the peak of the rapid filling wave of the apex cardiogram and occurred during the early diastolic closing motion of the anterior mitral leaflet. Although no opening snap (OS) was recorded on this phonocardiogram, the S_2–OS time interval measured on other phonocardiograms was the same as the S_2–OS point time interval measured on this recording.

Figure 5 shows simultaneously recordings of the electrocardiogram, external phonocardiogram and echocardiogram. The latter demonstrated the dimensions of the right and left ventricles, and the thickness of the interventricular septum (IVS) and left ventricular posterior wall (LVPW). The ventricular septum was abnormally thick, measuring 1.9 cm in thickness. The left ventricular posterior wall was normal in thickness, measuring 1.0 cm. The IVS/LVPW ratio was 1.9:1.0. In normal persons and in patients with fixed left ventricular outflow obstruction this ratio is less than 1.3; in patients with asymmetric septal hypertrophy this ratio is 1.3 or greater.[2] The right and left ventricular dimensions were within normal limits.

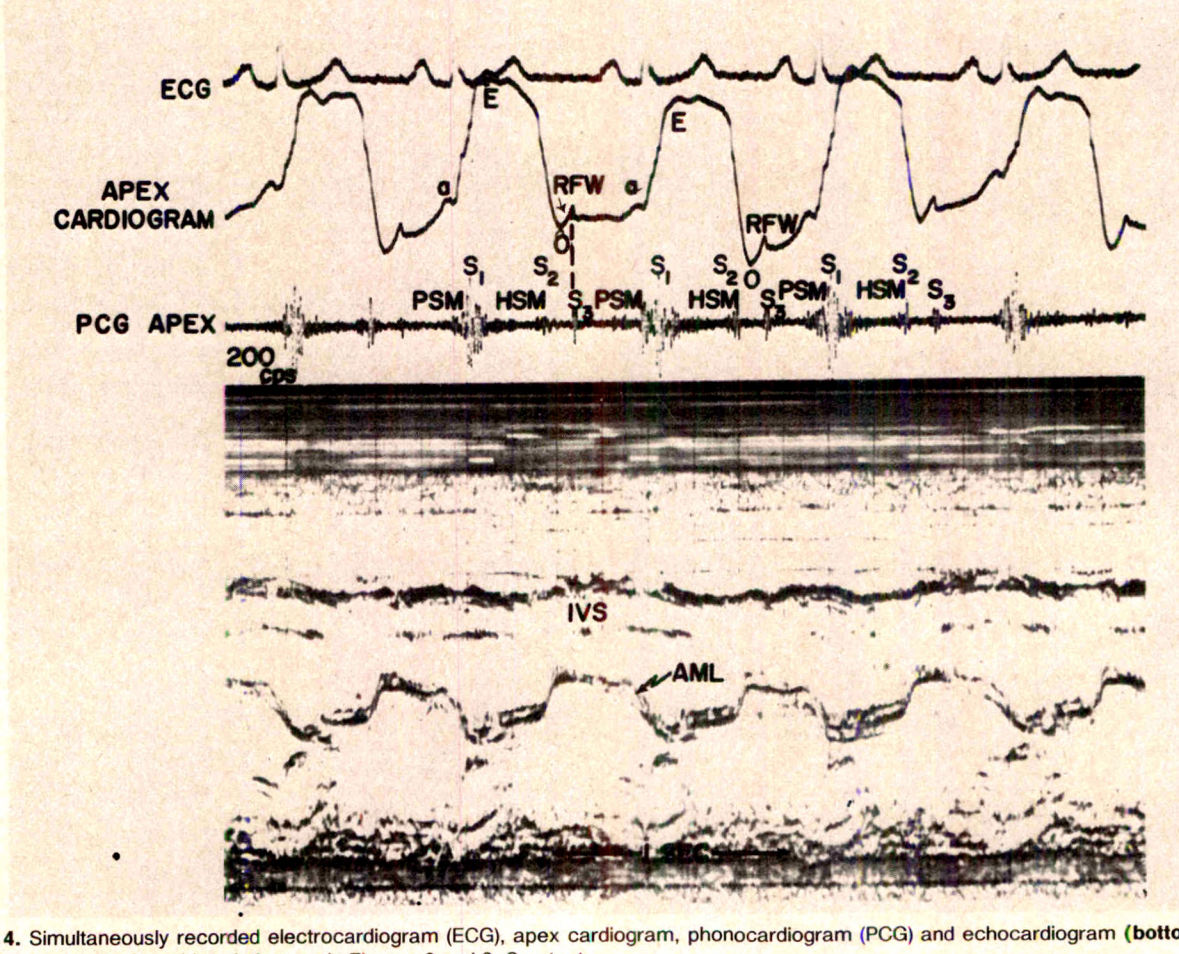

FIGURE 4. Simultaneously recorded electrocardiogram (ECG), apex cardiogram, phonocardiogram (PCG) and echocardiogram **(bottom).** RFW = rapid filling wave. Other abbreviations as in Figures 2 and 3. See text.

Cardiac Catheterization and Intracardiac Sound Findings

The following pressures (in mm Hg) were recorded: mean right atrial 5 (*a* wave 8; *v* wave 7), right ventricular 33/8 (post-*a* wave) and pulmonary arterial 29/15 (mean 21). The mean pulmonary capillary wedge pressure was 13 (*a* wave 18; *v* wave 17) and simultaneously recorded left ventricular pressure 95/13. The mean diastolic pressure gradient calculated from the phasic pulmonary capillary wedge and left ventricular pressure recording was 3. The upper limit of normal in our laboratory is 5 and the mean mitral diastolic gradient remained below this limit during infusion of isoproterenol. Subsequent simultaneous

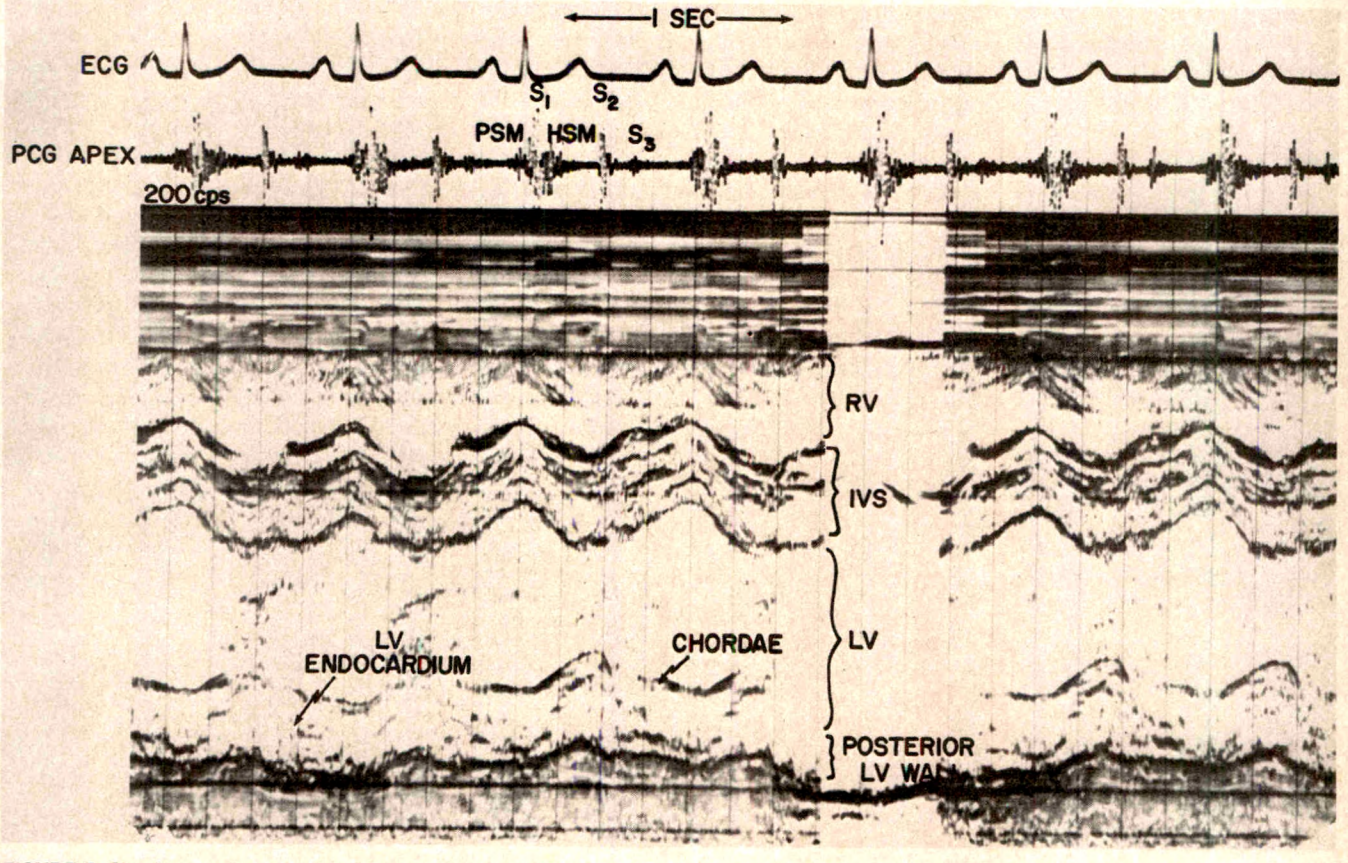

FIGURE 5. Simultaneously recorded electrocardiogram (ECG) phonocardiogram (PCG) and echocardiogram **(bottom).** See text. LV = left ventricle; RV = right ventricle. Other abbreviations as in Figures 2 and 3.

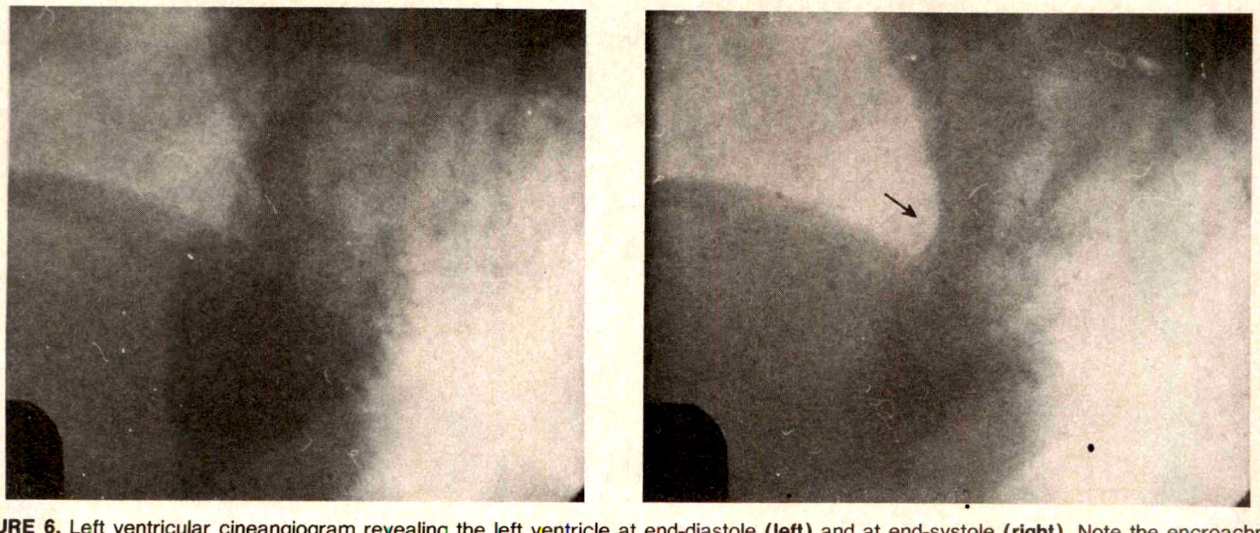

FIGURE 6. Left ventricular cineangiogram revealing the left ventricle at end-diastole **(left)** and at end-systole **(right).** Note the encroachment during systole on the left ventricular cavity of the thickened interventricular septum **(arrow).**

left ventricular inflow tract and brachial arterial pressure recordings revealed no systolic left ventricular outflow gradient; no outflow pressure gradient appeared during postextrasystolic beats or during the intravenous infusion of isoproterenol. The left ventricular end-diastolic pressure remained 13 during administration of isoproterenol. The resting cardiac index was 3.0 liters/min per m^2.

A left ventricular cineangiogram (Fig. 6) revealed abnormal thickening of the superior portion of the ventricular septum and septal encroachment upon the left ventricular cavity. The anterior leaflet of the mitral valve impinged only slightly upon the left ventricular outflow tract during systole. This questionable finding is not seen in Figure 6. Mild mitral regurgitation was demonstrated.

Left ventricular sound and pressure events were recorded simultaneously with an echogram of the anterior leaflet of the mitral valve (Fig. 7). A presystolic murmur was recorded within the inflow tract and occurred while the anterior mitral leaflet was moving toward the closed position after atrial systole. A decrescendo holosystolic murmur was present, and an ejection sound was recorded 0.07 second after S_1. A loud opening snap was recorded 0.10 second after S_2 and, as in Figure 3, coincided with the E point of the anterior mitral leaflet. A mid-diastolic murmur was seen on the intracardiac sound recording and occurred when the mitral valve was moving posteriorly toward a closed position after the early diastolic phase of ventricular filling.

Discussion

The history, physical examination, electrocardiogram and roentgenographic findings in our patient strongly suggested a diagnosis of rheumatic heart disease with combined mitral stenosis and insufficiency. Her symptoms of exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea and pedal edema in association with a loud S_1, apical presystolic murmur and opening snap favored mitral stenosis as the dominant lesion. The left atrial enlargement revealed on the electrocardiogram, chest roentgenogram and barium esophogram was consistent with this diagnosis. An apical systolic murmur is common in "pure" mitral stenosis, and is the rule in mixed mitral valve lesions. Inconsistent with a diagnosis of dominant mitral stenosis were the complaint of angina pectoris, without signs of significant pulmonary hypertension, and the evidence of left ventricular enlargement. Without evidence of significant mitral incompetence, aortic valve disease or systemic hypertension, these findings should have suggested additional myocardial disease or primary idiopathic myocardial disease.

The clinical findings in patients with hypertrophic cardiomyopathy or asymmetric septal hypertrophy

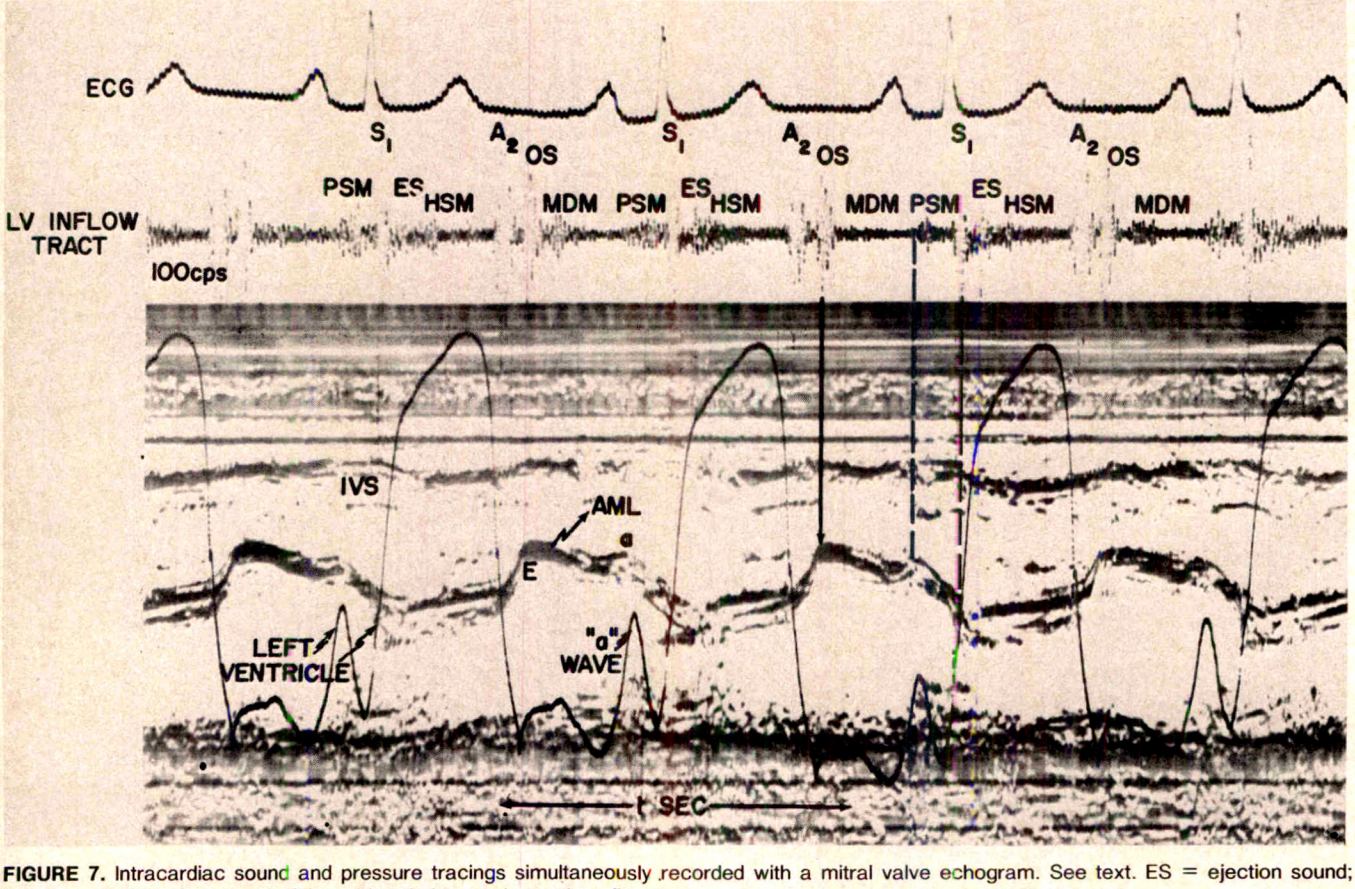

FIGURE 7. Intracardiac sound and pressure tracings simultaneously recorded with a mitral valve echogram. See text. ES = ejection sound; MDM = mid-diastolic murmur. Other abbreviations as in previous figures.

have been extensively described.[1–8] It is well known that asymmetric septal hypertrophy with left ventricular outflow tract obstruction must be distinguished from valvular aortic stenosis.[3] Although apical rumbling and blowing diastolic murmurs have been described in obstructive cardiomyopathy, the clinical findings related to outflow tract obstruction are usually dominant. The three patients of Shabetai and Davidson[5] had no outflow tract obstruction but had an apical rumbling diastolic murmur and a third heart sound gallop that was mistaken for an opening snap. Only one of their patients had a presystolic murmur. Our patient had similar clinical findings and we found a mitral opening snap in addition to the S_3 gallop (Fig. 2 and 3). The opening snap was confirmed by intracardiac phonocardiogram. Our patient's clinical findings simulate mitral stenosis more closely than has been reported previously.

Shabetai and Davidson[5] stated that echocardiography was not helpful in diagnosing "inflow-tract obstructive cardiomyopathy" and stressed the need for invasive hemodynamic studies to clarify the diagnosis. In our patient noninvasive studies were crucial: The phonocardiogram (Fig. 2) clarified the auscultatory findings, and the combined phonocardiographic and echocardiographic recordings (Fig. 3 and 5) led us to the correct diagnosis.

Echocardiographic findings: Recent reports[2,9,10] have shown echocardiography to be a sensitive and reliable noninvasive means of diagnosing obstructive and nonobstructive hypertrophic cardiomyopathy. The diagnostic marker in the spectrum of hypertrophic cardiomyopathy disease is asymmetric septal hypertrophy, which can be reliably detected by echocardiography.[2,11] The echocardiographic diagnosis of asymmetric septal hypertrophy without obstruction[9,11] depends upon an increased thickness of the interventricular septum (IVS) with a normal or increased left ventricular posterior wall (LVPW) thickness, decreased velocity of the early diastolic closing slope of the anterior mitral leaflet and lack of an abnormal anterior systolic motion of the mitral leaflets as is found with outflow tract obstruction. The IVS/LVPW ratio in asymmetric septal hypertrophy exceeds 1.3:1.0.[2,11] In our patient there was marked thickening of the interventricular septum and a normal left ventricular posterior wall thickness. The IVS/LVPW ratio was 1.9:1.0 (Fig. 4). The mitral valve diastolic slope was 19 mm/sec, and there was no abnormal anterior systolic motion of the mitral leaflets (Fig. 3). Asymmetric septal hypertrophy is sometimes found in patients with severe right ventricular hypertension,[2] but there was no clinical or hemodynamic evidence of the latter in our patient.

The diagnostic echocardiographic findings in mitral stenosis are well known.[12–14] The diminished velocity of diastolic closure of the anterior mitral leaflet echo in asymmetric septal hypertrophy is similar to that seen in mitral stenosis. However, in the former disease, the motion of the posterior mitral leaflet echo is normal whereas in mitral stenosis there is abnormal anterior motion of this leaflet echo.[14] The normal posterior mitral leaflet motion excluded a diagnosis of mitral stenosis (Fig. 3).

Origin of the opening snap: The auscultatory findings in our patient were further clarified by simultaneously recording a phonocardiogram with the echocardiogram. The sound labeled opening snap (OS) coincided with the point of maximal diastolic opening of the anterior mitral leaflet (Fig. 3 and 7). Angiographic studies in patients with mitral stenosis have revealed the opening snap to be temporally related to the abrupt halt of the mitral valve at its maximal diastolic excursion.[15] An anatomically abnormal or thickened mitral leaflet apparently is needed to produce the opening snap. Roberts[16] described thickening of the anterior mitral leaflet in 24 of 32 patients with hypertrophic cardiomyopathy and listed this feature as one of the characteristic anatomic findings. We suggest that in our patient with asymmetric septal hypertrophy an alteration in mitral leaflet position due to papillary muscle malalignment by a hypertrophied septum led to leaflet thickening[16]; it is possible that the opening snap was produced by sudden halting of this thickened leaflet at its point of maximal diastolic excursion during ventricular filling. The intracardiac phonocardiogram (Fig. 7) recorded the opening snap in the left ventricular inflow tract. There was no evidence of either severe mitral incompetence or a left to right shunt, two other conditions in which an opening snap may occur.

The sound labeled S_3 (Fig. 2 and 3) occurred 0.16 second after S_2 and coincided with the peak of the rapid filling wave of a simultaneously recorded apex cardiogram (Fig. 4). An S_3 gallop and murmur of mitral regurgitation (Fig. 2, 3 and 7) frequently occur in hypertrophic cardiomyopathy with outflow obstruction,[6] but may also be present in the absence of obstruction.

Left ventricular inflow tract obstruction: Goodwin and his co-authors[1,6,7] have emphasized that inflow tract obstruction is an important component of the pathophysiology of hypertrophic cardiomyopathy. That the alterations are due to diminished diastolic compliance of the left ventricular myocardium and not to a discrete zone of left ventricular inflow obstruction was shown in our patient by the absence of a significant diastolic pressure gradient between the pulmonary capillary wedge and left ventricular inflow tract during cardiac catheterization. Shabetai and Davidson[5] reported similar findings in their patients. Stewart et al.[17] showed that in obstructive cardiomyopathy left ventricular filling was slowed, as measured by the *Y* descent of the left atrial pressure recording. Impedance to left ventricular filling could be explained by any combination of diminished myocardial compliance, septal hypertrophy and thickening of the anterior mitral leaflet. The impedance to filling would account for the prominent *a* wave equivalent in the left ventricular pressure tracing (Fig. 7). This finding suggests that atrial contraction contributed significantly to

filling of the left ventricle in late diastole. The presystolic murmur occurred while the mitral leaflets were moving to the closed position after atrial systole (Fig. 3 and 7). These findings are consistent with Fortuin and Craige's explanation[18] of the genesis of mitral diastolic murmurs.

The hemodynamic and angiographic studies in our patient confirmed the diagnosis of asymmetric septal hypertrophy without outflow tract obstruction. Of note in the hemodynamic study of our patient was the failure of left ventricular end-diastolic pressure to increase during infusion of isoproterenol. Webb-Peploe[19] showed that this pressure increases in response to beta adrenergic stimulation in patients with hypertrophic cardiomyopathy, whereas it decreases in patients with other forms of heart disease and in normal subjects. This effect is independent of heart rate and probably reflects an alteration in diastolic relaxation of the left ventricle. We have no explanation for the anomalous response to isoproterenol in our patient.

We concur with Shabetai and Davidson[5] that patients with asymmetric septal hypertrophy may have clinical findings that mimic mitral stenosis and we agree that appreciation of this syndrome is essential to avoid potentially disastrous surgical therapy. Our case emphasizes the usefulness of noninvasive techniques in determining the correct diagnosis and is the first reported instance of asymmetric septal hypertrophy in which the presence and origin of an opening snap were documented by intracardiac phonocardiography.

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Primary Cardiomyopathy in Identical Twins

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Seventeen year old identical twin brothers with no family history of cardiopathy began experiencing palpitations almost simultaneously. In both, examination revealed marked cardiomegaly and hypokinesia of the ventricular walls, and clinical and radiologic signs of progressive cardiac failure developed a few days later. Both boys died suddenly, 49 days and 5 months, respectively, after the initial examination. Electrocardiographic and vectorcardiographic studies revealed a severe intraventricular conduction disturbance that coincided with histologic changes in the myocardial tissue, including profuse interstitial fibrosis, hypertrophy and degeneration of the myocardial fibers, aberrant arrangement of the muscular fibers and considerable alteration of the structure of cardiac tissue. In the absence of hereditary and chromosomal factors, and excluding possible viral intervention during fetal life, it is believed that a teratogenic factor can produce the structural alterations of the tissue and derangement of the fibers observed in these hearts.

The irregular contractions of the heart at the level of the net-like meshwork, disarrangement of myocardial fibers, and adaptative mechanisms of the heart inherent in the destruction of the contractile tissue contributed to the functional cardiac disorders that resulted in congestive heart failure and sudden death in these twins.

The lack of knowledge of the factors determining the histologic alterations of the heart and of the pathophysiologic mechanisms conditioned by the structural changes of cardiac tissue has led to much confusion about primary cardiomyopathies. Evans,[1] in the first report of familial cardiomyopathy, included four cases without a familial antecedent. Coelho et al.[2] described nine members of a family with cardiac enlargement, one studied post mortem, and reported autopsy data in another case, not familial. The macroscopic and microscopic findings in the heart were similar in both autopsy cases. Two autopsy cases reported by Campbell and Turner-Warwick[3] from two different families with familial cardiomegaly manifested different histopathologic findings: In the first case there were hypertrophy of the muscle fibers and dense plates of fibrotic tissue and in the second, hypertrophic myocardial fibers with hydropic vacuolation but without interstitial fibrosis. It is evident, therefore, that within this group of cardiomyopathies, some cases with identical histopathologic features are not of a familial nature, whereas some cases with a familial factor may manifest different histopathologic findings. These observations suggest that some common elements in the genesis of primary cardiomyopathy produce similar myocardial responses, whereas in familial cardiomyopathy several factors may condition different histopathologic reactions in the cardiac tissues.

In this study of cardiomyopathy in twin brothers we analyze the causes of the structural changes in the cardiac muscle and correlate

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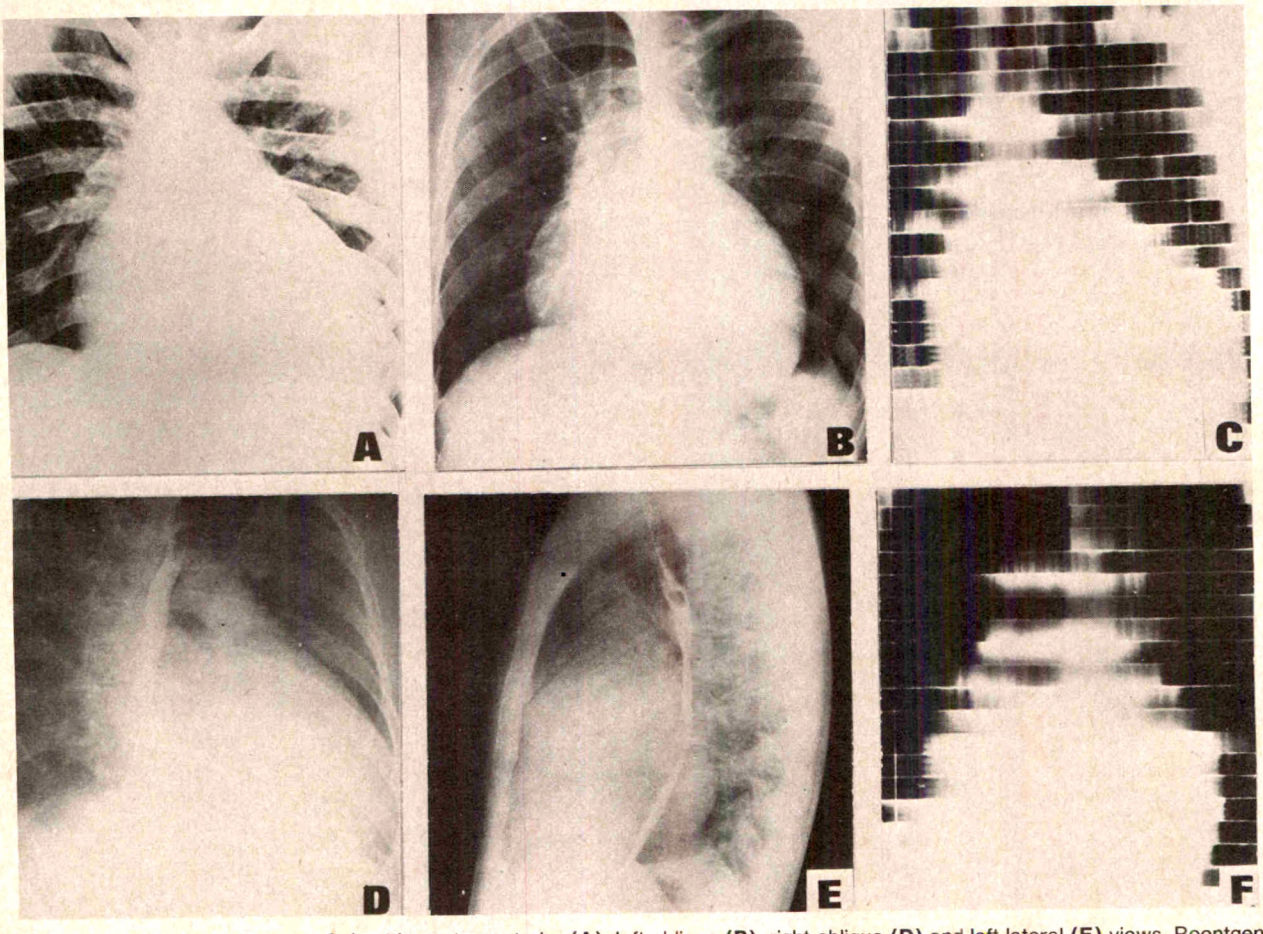


FIGURE 1. Case 1. Roentgenograms of chest in posteroanterior **(A)**, left oblique **(B)**, right oblique **(D)** and left lateral **(E)** views. Roentgenkymograms in posteroanterior **(C)** and left oblique **(F)** views.

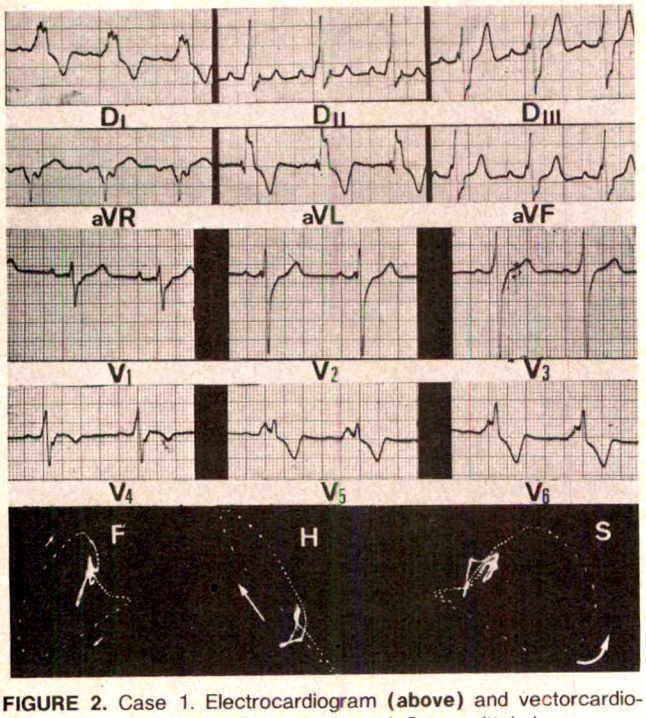


FIGURE 2. Case 1. Electrocardiogram **(above)** and vectorcardiogram **(below)**. F = frontal; H = horizontal; S = sagittal planes.

them with the clinical, radiologic and electrocardiographic data and the pathophysiologic mechanisms responsible for the clinical findings.

Report of Cases

Seventeen year old male monozygotic twins born after a normal full-term pregnancy and delivery were studied. They were the only male offspring of young and healthy parents who had no significant findings, personal or hereditary, related to cardiovascular disease. The only sibling, a 16 year old sister, is healthy. Results of karyograms, including culture, taken from five members of this family, a general and cardiovascular examination of the parents and the sister, including roentgenogram, karyogram, electrocardiogram, vectorcardiogram, phonomechanocardiogram, hematologic study, blood chemistry determinations and complement fixation test to Trypanosoma cruzi, were all normal.

The twin subjects of this study underwent, in addition to these studies, follow-up examinations and a complete postmortem study. A coronary arteriogram was obtained immediately after death. Both patients were high school students, active in sports and had a healthy appearance and normal physical development. At age 6 years, a cardiac arrhythmia was discovered but no special importance was attached to it at the time.

Case 1: Patient 1 had mild dyspnea and frequent palpitations that appeared abruptly, generally during routine

activity, and lasted for several seconds to 24 hours. Physical examination disclosed moderate jugular distension; diminished intensity of the first heart sound at the apex; a loud second sound, split at the pulmonary area; a regular pulse, with sudden rise, bisferiens in type; and blood pressure of 110/70 mm Hg.

X-ray films (Fig. 1) revealed enlargement of the heart, particularly of the left ventricle, pulmonary capillary hypertension and diminished contraction of the left ventricle on roentgenkymogram.

The electrocardiogram (Fig. 2) indicated a serious disorder of intraventricular conduction and diffuse disturbance of ventricular repolarization.

The vectorcardiogram (Fig. 2) disclosed abnormal rotation of the QRS loop with delays of the initial and final segments, confirming a peripheral disorder in impulse conduction and disturbance in ventricular repolarization.

The carotid pressure pulse curves (not shown) showed a rapid ascent and very pronounced dicrotic notch, followed by a second ascent, as is observed in idiopathic hypertrophic subaortic stenosis.

These data suggested cardiomyopathy of the congestive type, with significant myocardial alterations.

Case 2: The brother was examined because of his twin's condition. He complained of recurrent palpitations of a few minutes' duration that appeared during moderate exercise; he also noted dyspnea on exertion, which had not been considered significant. Physical examination revealed diminished intensity of the first heart sound at the apex; a loud second sound at the pulmonary area, a bisferiens pulse and blood pressure of 115/70 mm Hg. The carotid pressure pulse curve was similar to that of the twin.

X-ray films (Fig. 3) revealed enlargement of the heart and pulmonary hypertension. Fluoroscopic examination disclosed diminution of the amplitude of pulsation over the left ventricle.

The electrocardiogram (Fig. 4) showed a tall R wave and slurring of the ascending limb in the right precordial leads, suggesting a serious disorder of intraventricular conduction and diffuse disturbance of ventricular repolarization.

The vectorcardiogram (Fig. 4) disclosed the absence of activation in the anteroinferior zone of the left ventricle, and irregularities and posterior-superior displacement of the QRS loop, thus confirming the severe intraventricular conduction disturbance and alteration of ventricular repolarization.

Clinical course: Although the clinical findings in the brothers were apparently similar—both had negative results of a complement fixation test to Trypanosoma cruzi and normal hematologic and blood chemistry values—the clinical course in the two cases differed. Several episodes of cardiac failure developed in Patient 2 despite a regimen of digitalis, diuretic agents and a low salt diet. He had several severe episodes of ventricular arrhythmias and paroxysmal tachycardia and died suddenly. Patient 1 had several episodes of cardiac failure that were treated in the usual fash-

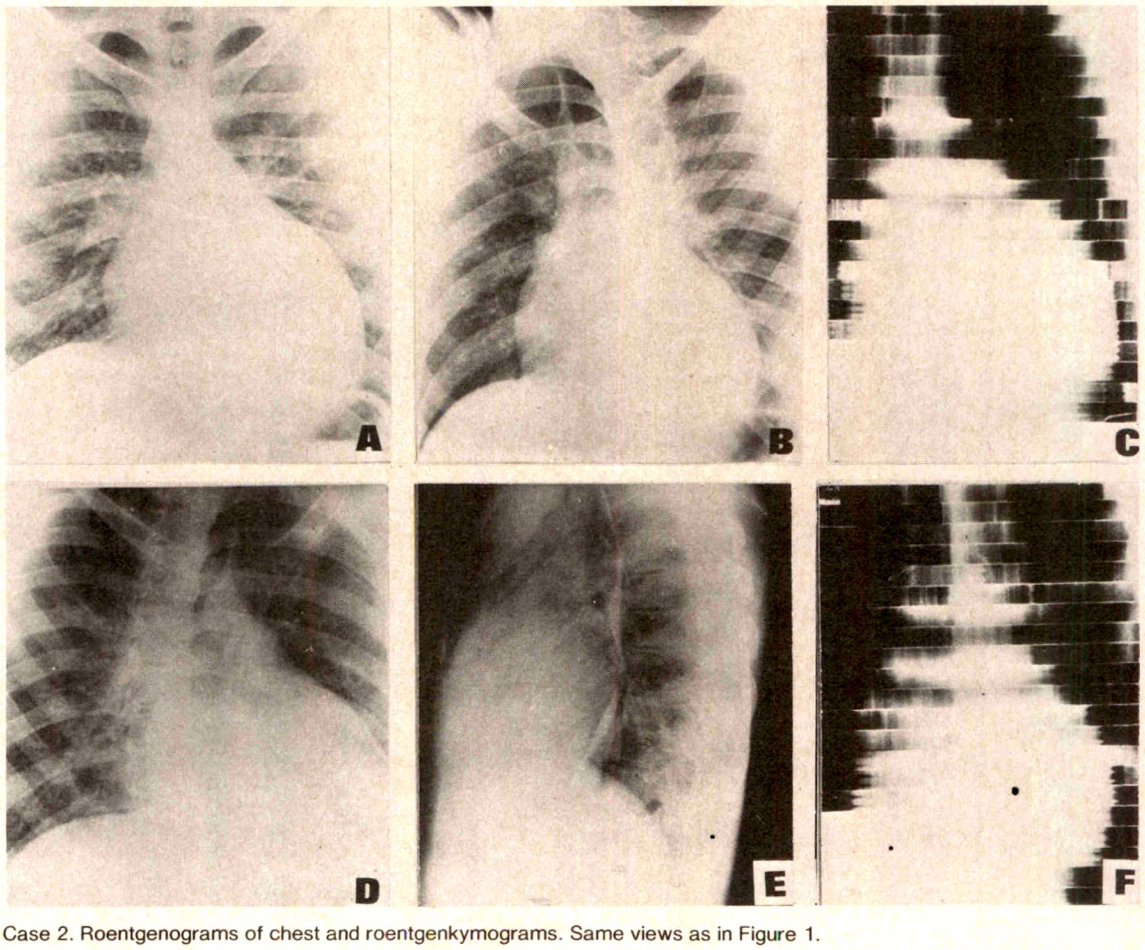


FIGURE 3. Case 2. Roentgenograms of chest and roentgenkymograms. Same views as in Figure 1.

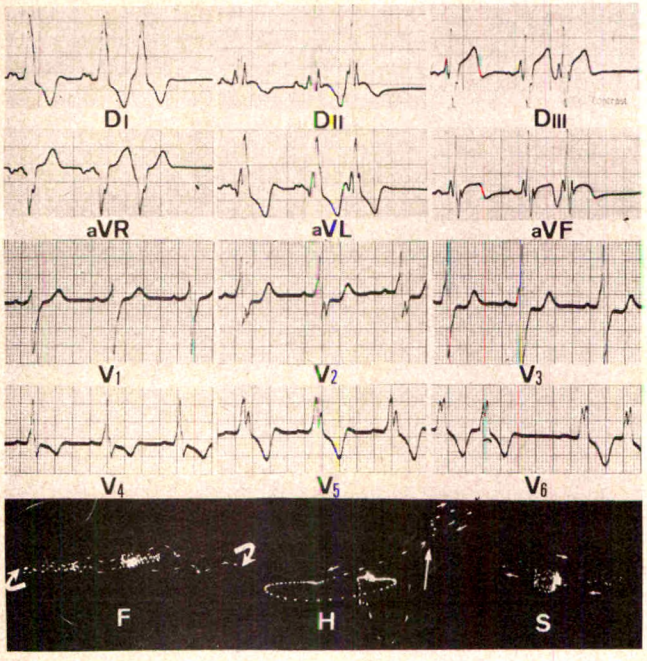


FIGURE 4. Case 2. Electrocardiogram **(above)** and vectorcardiogram **(below).**

ion. He also had supraventricular arrhythmias on several occasions, atrial fibrillation and sinus rhythm, with premature atrial beats. He died suddenly 3 months after his brother.

Pathologic Findings

Both patients had chronic congestion and edema of the lungs, passive congestion of the abdominal viscera, and increased caliber of the pulmonary artery and outflow tract of the right ventricle. Both had advanced cardiomegaly (Fig. 5 and 6) with dilatation and hypertrophy of all cardiac chambers and thickening of the ventricular walls. In Case 1 left ventricular wall thickness was 16 mm at the base of the heart, 15 mm at the apex; the ventricular septum measured 18 mm in the anterior area of the base, 14 mm in the posterior area of the base of the septum and 20 mm in the apical section of the septum; in the right ventricle the base measured 5 mm and the apex 4 mm. In Case 2 the measurements of the left ventricular free wall were as follows: anterior area of the base 17 mm, posterior area 15 mm, the middle third (between base and apex) 14 mm in both the anterior and posterior areas and 10 mm at the apex. The right ventricular free wall measured 7 mm at the base and 5 mm at the apex. The mitral valve manifested no lesion. There were no endocardial plates in the outflow tract of the left ventricle.

Several sections of the heart muscle demonstrated small scars scattered in both ventricles but no widespread plates of fibrous tissue. In Case 1 one area of the apex of the left ventricle was reduced to a thickness of 2 mm. Although there was no disease of the coronary arteries, collateral circulation was increased (Fig. 5B and 6B).

Microscopic study (Fig. 7) disclosed interstitial fibrosis. Myocardial areas were replaced by fibrous tissue, without inflammatory infiltrations. Tracts of myocardial fibers, included in the fibrotic plates, showed degenerative changes (Fig. 7B).

In Case 2, the most important finding was the aberrant arrangement of the muscular fibers, which intertwined and showed definite changes in direction, forming whorls. This aberrant pattern altered the structure of cardiac tissue (Fig. 7, A and C) at the level of the free walls of the left ventricle and in the interventricular septum. In Case 1 the arrangement of the fibers was not altered, but there were hypertrophic muscular fibers with vacuolar degeneration and important nuclear changes (Fig. 7D) at the level of the free walls of both ventricles.

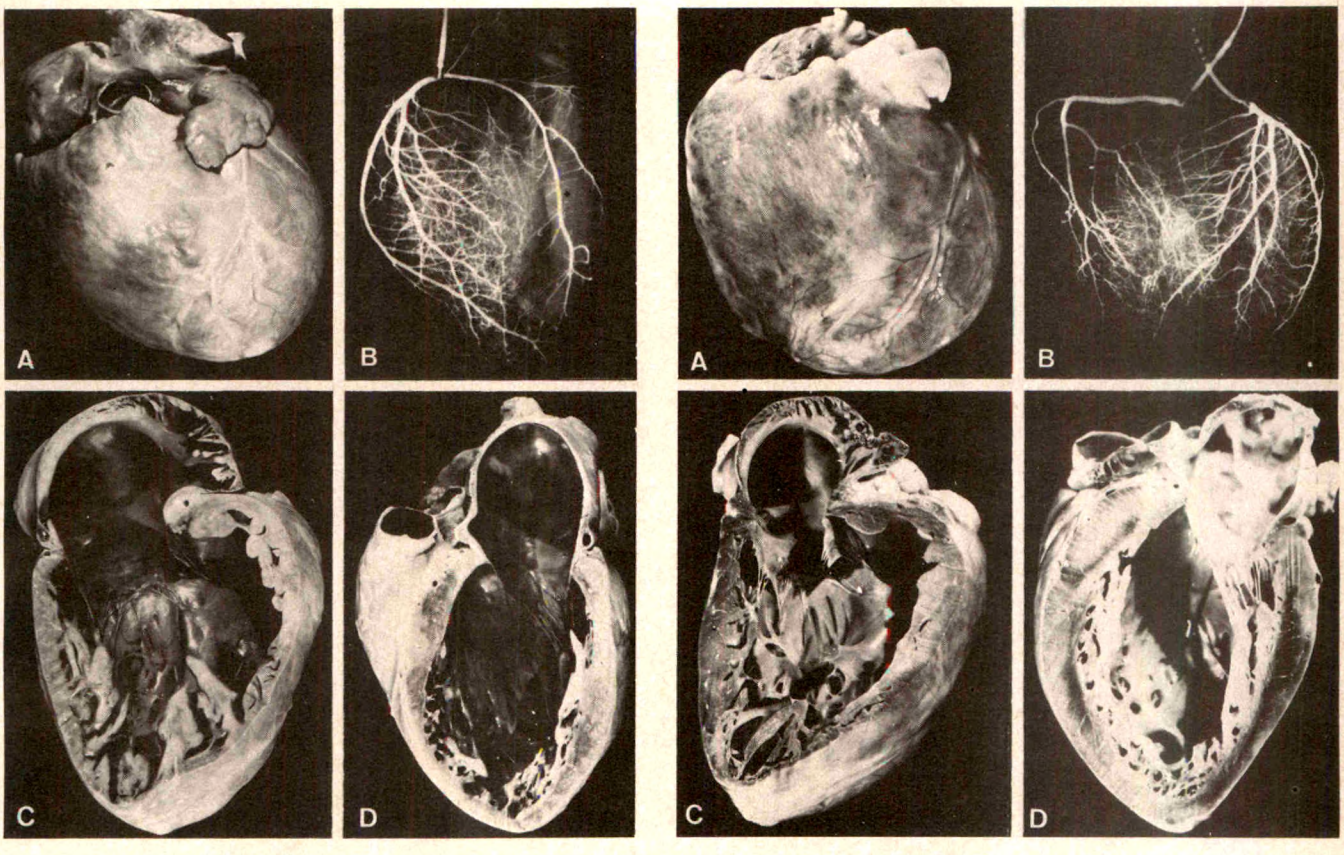
Discussion

The clinical findings in these twins are consistent with cardiomyopathy of the congestive type, with serious myocardial alterations and disorders of intraventricular conduction. The personal history, the absence of epidemiologic factors (Chagas' disease) and negative serologic reaction to Trypanosoma cruzi, the laboratory findings, and the physical examination rule out a cardiomyopathy secondary to an infectious, toxic, metabolic or nutritional process, or one associated with neuromuscular disorders or systemic disease. In the absence of coronary artery disease, it is possible that some instances of diffuse myocardial fibrosis may be due to an inapparent, single or recurrent Coxsackie viral infection. Although this mechanism could explain the diffuse myocardial fibrosis, it would not account for the alterations observed in the structure of the tissue in one case and we therefore consider a primary cardiomyopathy the more likely diagnosis. The absence of familial antecedents and results of the karyogram rule out a hereditary or chromosomal factor. The picornavirus group has been held responsible for a highly cardiotropic action in the fetus in utero, resulting in cardiac anomalies and stillbirth.[4] However, at this stage the cardiac muscle is already formed in the fetus and viral action can destroy the contractile tissue and stimulate fibroblastic proliferation, but it cannot alter the structural arrangement of the tissue, as was observed in our Case 2 and in the case reported by Alatriste et al.[5]

After elimination of the familial factor as a cause for the primary myocardial disease in our two cases, the factors altering the arrangement of the heart muscle fibers remain to be analyzed. It is worth pointing out that a myocardial structural alteration is possible only in early embryonic life when the cardiac muscle is still being formed. We therefore believe that unknown teratogenic factors intervened during this early period and that the cardiomyopathy in our two cases had a common, probably congenital, origin.

Oakley[6] found fundamental histologic differences in cardiac muscle obtained during ventriculotomy from patients with hypertrophic cardiomyopathy and by open biopsy from patients with congestive cardiomyopathy. In the former, the myocardial fibers were abnormally short and wide, and were bizarrely arranged. These changes were absent in the patients with congestive cardiomyopathy, whose hypertrophied myocardial fibers resembled more closely those of myocardial hypertrophy from any cause. Histologic study in our cases revealed characteristics common to these types of cardiomyopathy. In one twin the structural arrangement of the tissue was altered, as

in hypertrophic cardiomyopathy; in the other twin, hypertrophy of the fibers and other features of congestive cardiomyopathy were evident. These findings suggest that the same teratogenic factor can produce different reactions in the cardiac tissue of the embryo. The anatomic-pathologic study in our cases showed hypertrophy of both ventricles; in the septum the apical zone was thicker than the basal zone. There was no fibrous plaque in the endocardium at the outflow tract of the left ventricle, and the tract



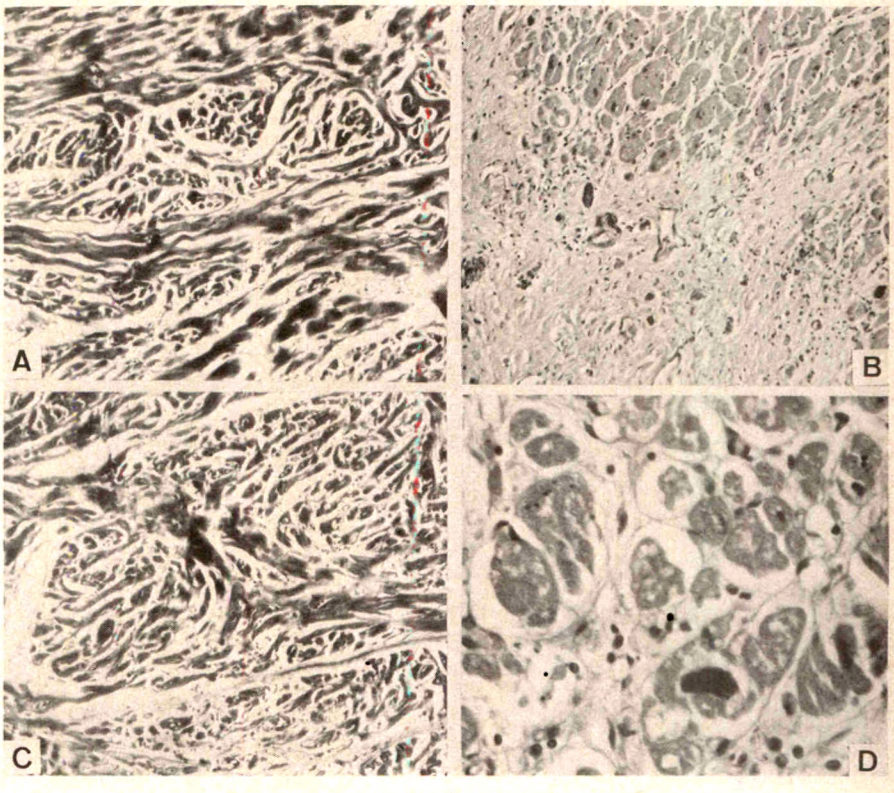


FIGURE 5 (upper left). Case 1. Postmortem specimen of heart. **A,** anterior aspect. **B,** coronary angiogram. **C,** section of right chambers. **D,** section of left chambers.

FIGURE 6 (upper right). Case 2. Postmortem specimen of heart. Panels **A** to **D** correspond to panels **A** to **D** in Figure 5.

FIGURE 7 (lower right). Microscopic sections of myocardium. **A** and **C,** Case 2. **B** and **D,** Case 1. See text. **A,** Gomori-Wheatley stain × 160; **B** and **C,** hematoxylin-eosin × 160; **D,** hematoxylin-eosin × 400; all reduced by 37 percent.

was amply proportioned in relation to the size of the ventricular chamber. All these facts argue against the possibility that idiopathic hypertrophic subaortic stenosis evolved in a congestive form.[7]

Meesen[8] found irregular contraction of the fibers and signs of distorted arrangement of the structure of hypertrophied cells in cases of idiopathic cardiomyopathy. Such irregularities of contraction diminish the function of the fiber in situ, producing an overactivity of nonaffected regions, similar to that described by Meerson[9] around the areas with myocardial infarction. The response to such hyperfunction affects the nucleic acid and protein synthesis in the myocardial cells, leading to hypertrophy of the fiber and, much later, to chronic cardiac failure.[9]

In addition to these pathophysiologic mechanisms analyzed in our two cases, destruction of the contractile tissue by inflammatory processes and its replacement by fibrotic tissue play an important role in the pathogenesis of cardiomyopathies.[10]

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Internal Mammary Arteriovenous Malformation with Communication to the Pulmonary Vessels

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A 25 year old asymptomatic man with a past history of pulmonary tuberculosis presented with a continuous murmur. Selective arteriography revealed a left internal mammary arteriovenous malformation in communication with vessels in the left upper pulmonary lobe. No significant hemodynamic abnormalities were detected. This is the 26th reported case of internal mammary arteriovenous fistula and the 6th with a pulmonary communication. Review of the data in previous cases suggests that surgical indications are limited to symptomatic relief, heart failure during infancy or the possible risk of endarteritis, proximal arterial degeneration or rupture.

Arteriovenous fistulas involving the internal mammary vessels are rare. Only 25 cases have previously been reported[1–21] and only 23 described in some detail.[1–19] In five cases the malformation communicated with the pulmonary vessels.[3,17–19] The following case represents the sixth report of this phenomenon.

Case Report

A 25 year old male laundry worker was admitted to the Boston City Hospital for evaluation of a continuous precordial murmur. At age 18, during a bout of "pneumonia and pleurisy," he was told he had tuberculosis and underwent 8 months of treatment with isoniazid at another institution. At age 23 he underwent tonsillectomy at that institution. He was not informed of a murmur during either hospitalization. The patient smoked 20 cigarettes daily and admitted having taken heroin intravenously two to four times a month for the past 18 months. His exercise tolerance was excellent, and he denied all cardiovascular and respiratory symptoms.

Physical examination revealed a robust, muscular young male. The vital signs were within normal limits, and no clubbing, cyanosis or telangiectasis was observed. The lungs were clear to auscultation, and the heart sounds were normal. A grade 3/6 high pitched continuous murmur was heard at the third and fourth intercostal spaces along the left sternal border. The murmur appeared to be close to the ear of the examiners.

Chest roentgenogram (Fig. 1) revealed small areas of calcification and linear densities in both upper pulmonary lobes. This finding as well as blunting of the left costophrenic angle was thought to represent old granulomatous disease. Results of a cardiac X-ray series with fluoroscopy and the electrocardiogram were normal. The hematocrit was 43 percent and several blood cultures yielded no growth.

At cardiac catheterization (Table I), intracardiac and pulmonary arterial pressures, cardiac output, and vascular resistance were normal except for slightly increased right ventricular systolic and end-diastolic pressures. An appropriate response followed leg-raising exercise. Measurement of blood oxygen saturation revealed no evidence of intracardiac or intrapulmonary shunting. The partial pressures of oxygen in systemic arterial blood responded to breathing of 100 percent oxygen by rising in normal fashion to a level of 650 mm Hg. Indocyanine green dye-dilution curves obtained by injection into the main pulmonary artery and aortic root and sampling, respectively, from the left brachial artery and main pulmonary arteries did not demonstrate abnormal initial appearance or early recirculation of dye. Main

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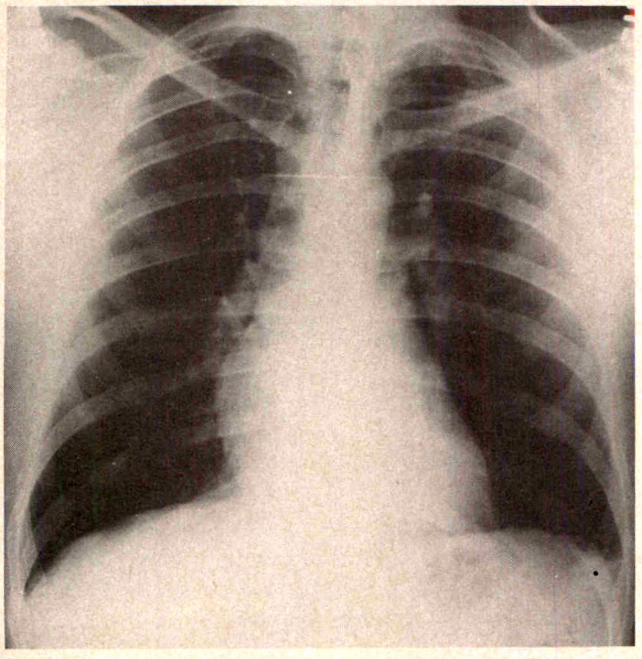

FIGURE 1. Chest roentgenogram, posteroanterior view. The internal mammary artery-pulmonary vessel fistula is seen immediately above the left pulmonary artery.

TABLE I

Results of Cardiac Catheterization

Site	Oxygen Saturation (%)	Pressure (mm Hg)* Rest	Pressure (mm Hg)* Exercise
Right atrium	81	(6)	
Right ventricle	80	32/8	
Pulmonary artery			
Main	80	(14)	(15)
Right	81		
Left	82		
Left ventricle		119/4	
Brachial artery	97	(104)	(115)
Heart rate (beats/min)		66	120
Oxygen consumption (cc/min)		199	850
Cardiac output (liters/min)		6.3	12.8
Cardiac index (liters/min per m^2)		3.2	6.6
Pulmonary vascular resistance (dynes sec cm^{-5})		127	69
Systemic vascular resistance (dynes sec cm^{-5})		1321	719

* Figures in parentheses indicate mean pressure; phasic pressures are expressed as peak systolic and end-diastolic values.

TABLE II

Five Previously Reported Cases of Internal Mammary (IM) Fistulas with Communication to the Pulmonary Vessels*

Authors	Patient's Age (yr) & Sex	Anatomic Description	Presenting Data
Bjork et al.[17]	23M	Left IM, phrenic, pericardiophrenic arteries to pulmonary veins	Continuous murmur
	25M	Left IM, phrenic, intercostal arteries to pulmonary veins	Continuous murmur
Voll et al.[18]	32F	Right IM artery to right pulmonary artery	Continuous murmur
Kiphart et al.[19]	23M	Right IM artery to right pulmonary artery	Continuous murmur, chest pain
Stafford et al.[13]	21F	Left IM artery to left pulmonary vessels	Continuous murmur, chest pain

* In all cases the lesion was congenital in origin and surgery was performed.

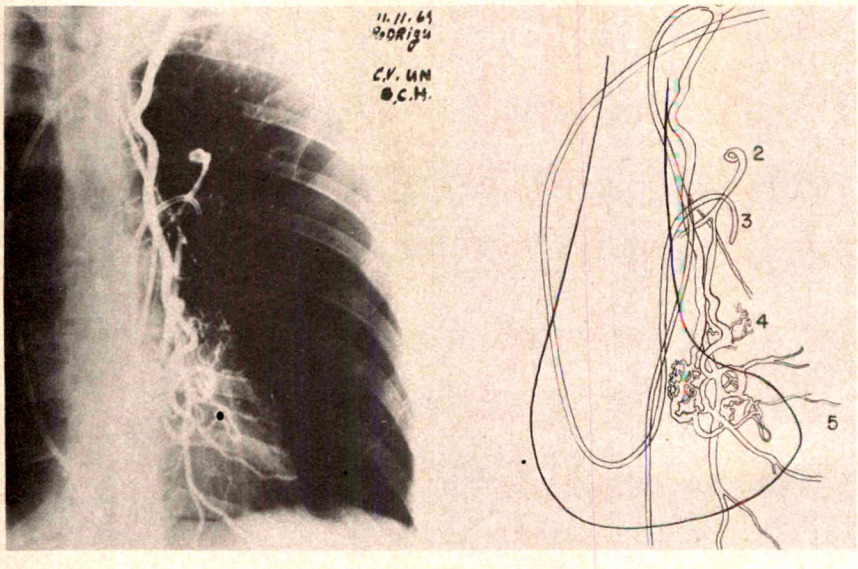

FIGURE 2. Selective left internal mammary arteriogram, anteroposterior view. **1,** catheter in the dilated proximal left internal mammary artery. **2,** fistula from the arteriovenous malformation to the left upper pulmonary lobe and site of entry into the pulmonary circulation. **3,** catheter in the left pulmonary artery. **4,** systemic arteriovenous malformation. **5,** intercostal branches of the left internal mammary artery.

and left pulmonary arteriograms revealed a 1 cm nodular area of opacification filling from the proximal left upper pulmonary artery and draining after a slight delay into the corresponding pulmonary vein. An aortic root arteriogram demonstrated a dilated proximal portion of the left internal mammary artery. A selective left internal mammary arteriogram (Fig. 2 and 3) revealed an extensive arteriovenous malformation at the level of the fourth rib with a late filling vessel coursing superiorly through the anterior mediastinum opacifying the same left upper lobe pulmonary nodule. Small pulmonary arterial radicles, identical to those visualized in the pulmonary arteriogram, emanated from this nodular area and coursed to the lung periphery. Drainage was by the same left upper lobe pulmonary vein, which was in direct communication with this nodule.

Despite the considerable risk of infectious endarteritis as a result of his heroin habit, the patient refused surgical intervention. Because of his lack of symptoms and relatively normal hemodynamic profile, he was discharged to follow-up in the clinic.

Discussion

Clinical and hemodynamic features: Thoracic arteriovenous fistulas are most commonly located in the lungs and cause left to right shunts that are sometimes symptomatic and associated with cyanosis, clubbing or telangiectasis.[22] Fistulas involving the vessels of the chest wall are rare, possibly because of the protected location of the vessels behind the bone structures of the thorax. Although systemic arteriovenous fistulas have been associated with increased blood volume, increased cardiac output and congestive heart failure when the involved vessels have been of large caliber, thoracic fistulas involving the internal mammary arteries have seldom caused severe symptoms in the adult. In the 16 adult cases without pulmonary communication previously reported in sufficient detail for evaluation, 5 patients had vague chest pain, 5 had various degrees of dyspnea and 3 had a pulsatile or expanding mass. There are two reports of congestive heart failure in infants with an internal mammary artery-ductus venosus communication,[5,14] but no adult has been reported to have cardiac decompensation attributable to a systemic internal mammary arteriovenous fistula. In the adult patient of Massumi[12] the shunt carried only 15 percent of the cardiac output. Intracardiac pressures, when measured, have invariably been normal.[6,9,10] This relative lack of hemodynamic significance is in marked contrast to the frequently striking physical finding of a continuous thoracic bruit occasionally mistaken for the murmur of a patent ductus arteriosus.[3,6,17]

The normal resting Fick cardiac output value in our case indicates a small shunt volume through the systemic internal mammary arteriovenous malformation. The normal response to 100 percent oxygen inhalation, the normal systemic arterial oxygen saturation and the lack of an oxygen step-up in intracardiac and pulmonary blood samples also imply insignificant or no pulmonary venoarterial, intracardiac or pulmonary-cardiac shunting. The slightly elevated values for pulmonary arterial systolic and right ventricular end-diastolic pressures may be due to our utilization of one half of the anteroposterior thoracic diameter as zero pressure reference point. This procedure has been observed to overestimate right heart pressure by as much as 3 mm Hg.[23] The arteriographic evidence that the internal mammary vessel fistula communicated predominantly with the left upper lobe pulmonary vein suggests the presence of a left to left shunt. The indicator-dilution curve, obtained by injection into the main pulmonary artery and sampling from the brachial artery, failed to demonstrate an early recirculation contour, thus attesting to the small volume of any such shunt. Further efforts at quantification, such as injection of indicator into the superior vena cava with simultaneous sampling from the pulmonary and brachial arteries,[24] were therefore not performed.

As in our case, the hemodynamic alterations were insignificant in the five previously reported cases of internal mammary arteriovenous malformations in communication with the pulmonary vessels (Table II). Although two of the patients experienced vague

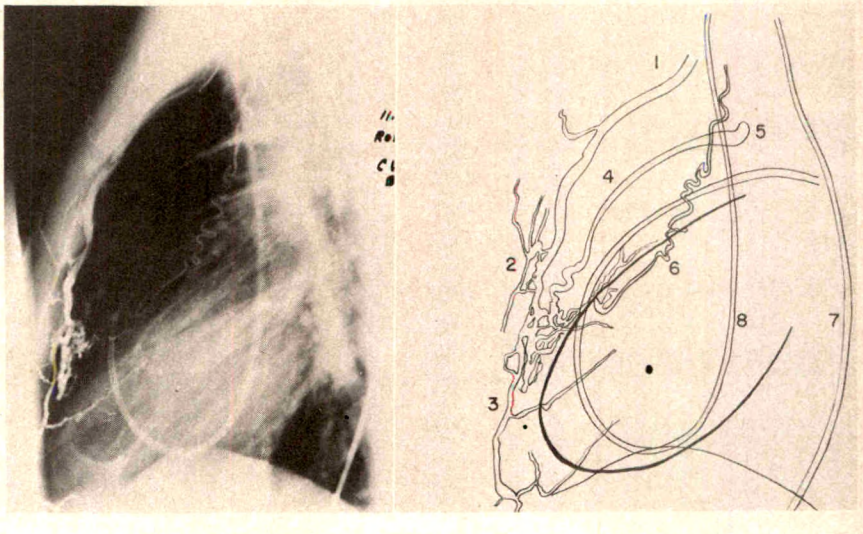

FIGURE 3. Selective left internal mammary arteriogram, lateral view. **1,** dilated proximal left internal mammary artery. **2,** arteriovenous malformation. **3,** distal internal mammary artery and its intercostal branches. **4,** fistula from the arteriovenous malformation to the left upper pulmonary lobe. **5,** entry site of the fistula into the pulmonary circulation. **6,** tortuous anterior mediastinal branch of the internal mammary artery. **7,** catheter to the internal mammary artery. **8,** catheter in the left pulmonary artery.

chest pain, and the patients of Voll et al.[18] and Kiphart et al.[19] had small oxygen increases at the pulmonary arterial level indicative of left to right shunting, no patient was reported to have cardiomegaly, increased intracardiac pressures[13,18,19] or increased cardiac output.[13] There have been a few reports of systemic artery-pulmonary vessel shunts, similar to the shunts in the aforementioned cases, involving vascular adhesions,[25] anomalous aortic branches,[26,27] intercostal arteries,[27,28] bronchial arteries,[27] coronary arteries[29] and other arteries of the chest wall.[30,31] Except in a few cases with large shunt volumes, these fistulas have been of little hemodynamic significance.

Etiology: The cause of these vascular anomalies is not always clear. Congenital, traumatic and inflammatory origins have been suggested. According to the early postulate of Lewis,[32] and on the basis of experience gained in previous cases, it is possible that congenital arteriovenous fistulas may not become manifest until adult life; this may have been the case in our patient, who gave no history of chest trauma. In view of the history and roentgenographic signs of left pulmonary and pleural tuberculosis, it is possible that the systemic-pulmonary communication had an inflammatory origin, similar to that in the patient described by Wolarsky.[28]

Surgical indications: The long-term prognosis of internal mammary arteriovenous fistulas with or without communication to the pulmonary vessels is unknown. Most reported cases have involved surgical ligation and excision. Despite the usually small shunt volume, complaints of local symptoms, or the risk of infectious endarteritis, rupture with intrathoracic or intrapulmonary hemorrhage or proximal arterial degeneration,[33] may justify surgical intervention. Medical follow-up of our patient will offer unique information on the natural history of this lesion.

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Progressive Pulmonary Vascular Disease After Surgical Correction (Mustard Procedure) of Transposition of Great Arteries with Intact Ventricular Septum

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Severe pulmonary vascular disease developed 1 year after a Mustard operation in a 2 1/3 year old boy with transposition of the great arteries and intact ventricular septum. The possible etiologic factors responsible for the development of pulmonary vascular disease are discussed, and it is suggested that this disturbing late postoperative complication may occur more frequently than is recognized.

The intraatrial baffle operation, as described by Mustard,[1] has been widely accepted as the definitive surgical procedure for children with transposition of the great arteries. In general, the results of this operation have been satisfactory. However, several immediate and late complications, including dysrhythmias, vena caval obstruction, pulmonary venous obstruction and tricuspid insufficiency, have been described.[2–5] In this report we record a case in which progressive pulmonary vascular disease, in the absence of pulmonary venous obstruction, developed in a boy with transposition of the great arteries and intact ventricular septum who underwent an apparently successful Mustard procedure and died 1 year later.

Case Report

A Filipino male infant was admitted for the first time on February 25, 1970 to Harbor General Hospital at age 3 weeks because of cyanosis and tachypnea. The product of a full-term, uneventful pregnancy and delivery with a birth weight of 7 lb, 2 oz, he was discharged from the nursery with no apparent problems. On admission, he was cyanotic and had rapid respirations. A grade 2–3/6 systolic murmur was heard at the lower left sternal border, and there was moderate hepatomegaly. The electrocardiogram revealed right ventricular hypertrophy. The chest roentgenogram disclosed an enlarged "egg-shaped" heart, with narrow supracardiac shadow and increased pulmonary vascularity. The infant was subsequently digitalized. Cardiac catheterization and angiocardiography revealed dextrotransposition of the great arteries, intact ventricular septum, patent foramen ovale and a small ductus arteriosus (Table I). Balloon atrial septostomy was performed with marked improvement in systemic oxygen saturation.

The patient underwent repeat cardiac catheterization at age 2 months because of progressive cyanosis and polycythemia (hematocrit 66 percent). The vena cava, right atrium and right ventricle all manifested severe oxygen desaturation; no intracardiac shunt was grossly detectable from the oxygen saturation data. Blood pressure was 92/0–4 mm Hg in the right ventricle and 52/0–5 mm Hg in the left ventricle. Neither the aorta nor the pulmonary artery was entered at that time. Because repeat balloon atrial septostomy resulted in only slight improvement in the patient's condition, atrial septostomy was performed 10 days later with use of the inflow occlusion technique. At operation a relatively large atrial septal defect, 1.5 cm in diameter, was noted and the remaining portion of the septum was excised.

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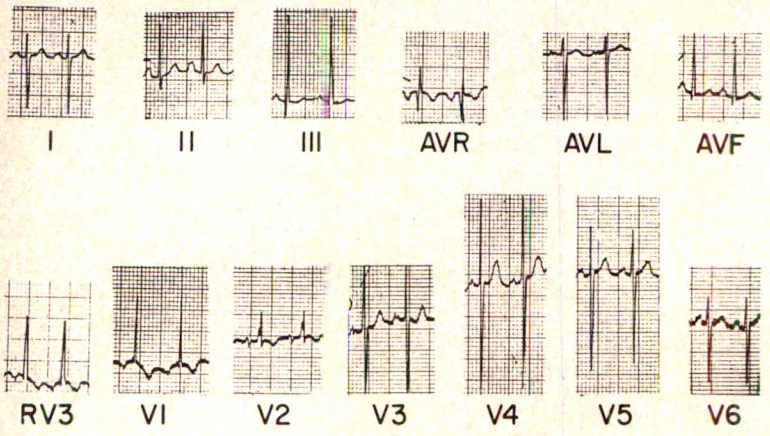

FIGURE 1. Electrocardiogram obtained immediately before the third cardiac catheterization (before the Mustard procedure) revealing right ventricular hypertrophy and evidence suggestive of biatrial hypertrophy.

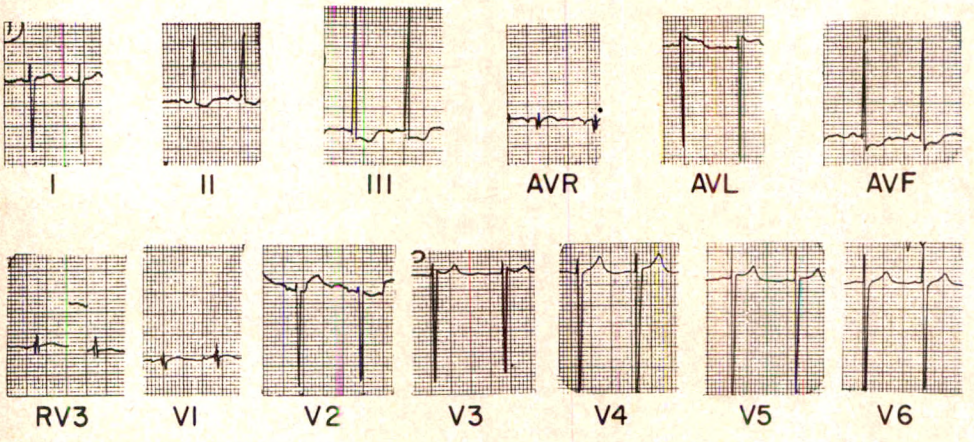

FIGURE 2. Electrocardiogram obtained 1 year after the Mustard procedure revealing prominent posterior and inferior forces compatible with severe left ventricular hypertrophy. Note S-T segment depression in leads III and aVF suggestive of subendocardial ischemia. The rsR′S′ in leads RV_3 and V_1 suggest the presence of additional right ventricular hypertrophy.

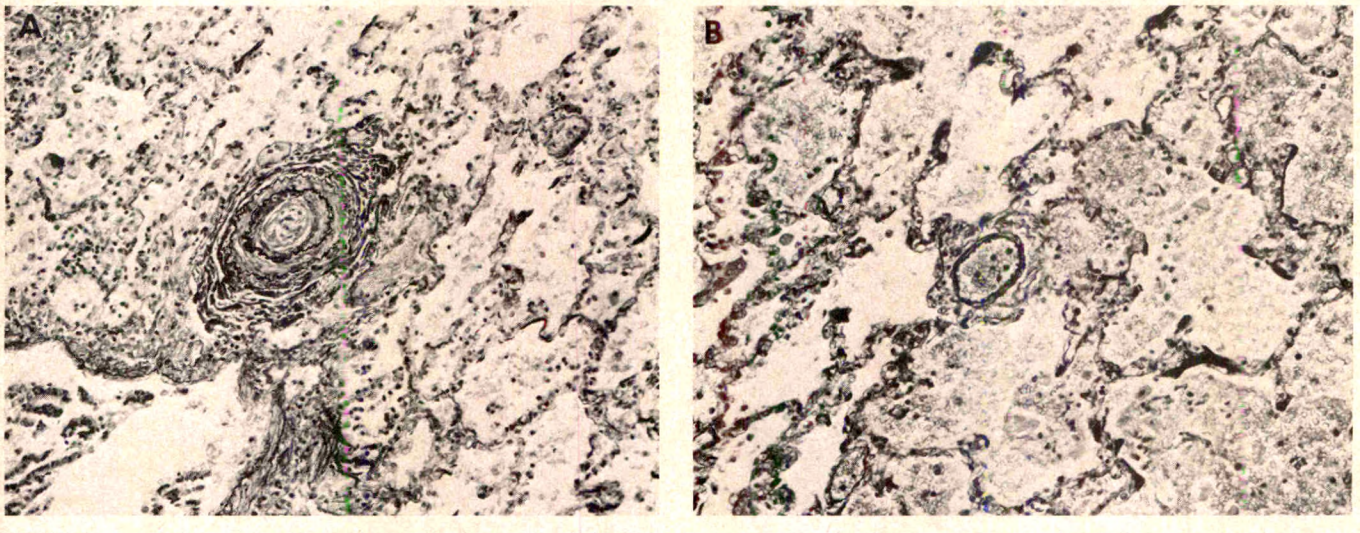

FIGURE 3. A, small muscular artery of lung showing marked intimal cellular and acellular proliferation and marked medial hypertrophy. **B,** control vessel of similar size from a child with no pulmonary hypertension. Note the thin media and high lumen to wall ratio characteristic of normal pulmonary arterial vessels. (Elastic-Van Gieson ×100, reduced by 23 percent.)

During the next few months the patient's condition was relatively stable; he gained weight slowly and his hematocrit ranged from 56 to 61 percent. Between the ages of 5 and 9 months, he required several hospitalizations for pneumonitis and viral syndromes associated with respiratory distress. On each admission the patient's hematocrit was noted to be increasing, and, by age 10 months, he was readmitted for severe cyanosis and respiratory distress associated with a hematocrit of 82 percent. After phlebotomy was performed, his condition improved and he was discharged with a hematocrit of 68 percent. One month later, he was readmitted for a third cardiac catheterization. Hematocrit was 70 percent and hemoglobin 22 g/100 ml. The electrocardiogram revealed right ventricular hypertrophy (Fig. 1). The study revealed marked aortic desaturation and moderate pulmonary hypertension. There was a small pressure gradient between the pulmonary artery and left ventricle (Table I). The estimated pulmonary to sys-

TABLE I

Serial Cardiac Catheterization Data

	Study no. 1 (age 1 mo.)		Study no. 2 (age 2 mo.)		Study no. 3 (age 11 mo.)		Study no. 4 (age 28 mo.)	
	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)
Superior vena cava	28	(4)	20	...	31	(3)	38	(15)
Right atrium	40	(4)	20	(2)	35	(3)	39	(17)
Right ventricle	39	88/0-7	21	92/0-4	42	82/0-6	...	...
Aorta	...	...			53	82/47(63)	...	...
Pulmonary vein	96	...	98	(4)	96	(4)	...	...
Left atrium	95	(6)	98	(4)	95	(3)	...	...
Left ventricle	91	...	98	52/0-5	84	54/0-3	33	125/4-18
Pulmonary artery					83	42/19(30)	...	...
After Balloon Septostomy								
Right ventricle	70	110/5-15	38	94/0-5				
Right atrium	70	...	...	...				
Left ventricle	91	110/0-6	...	...				

Figures in parentheses indicate mean pressures.
Sat = saturation.

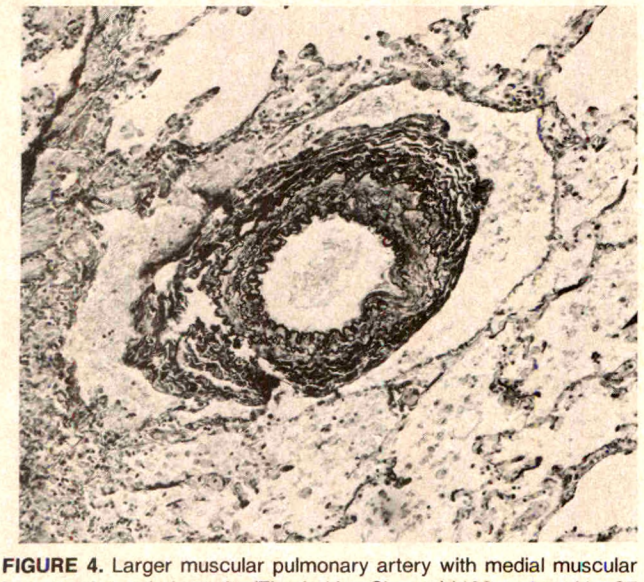

FIGURE 4. Larger muscular pulmonary artery with medial muscular hypertrophy and elastosis. (Elastic-Van Gieson ×100, reduced by 37 percent.)

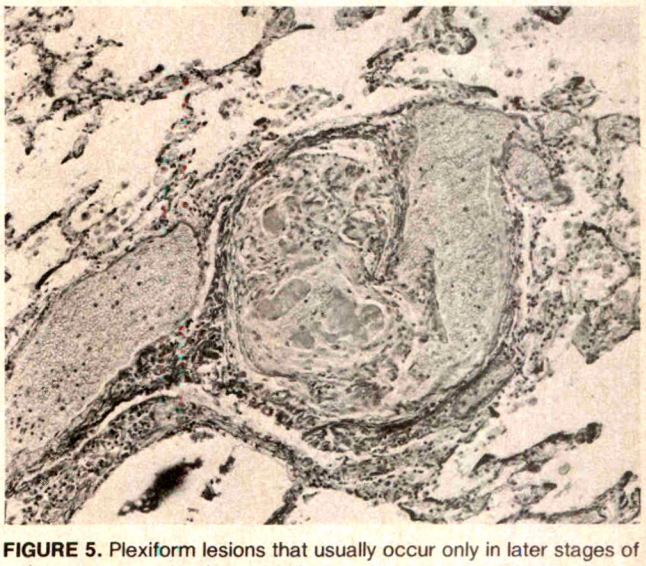

FIGURE 5. Plexiform lesions that usually occur only in later stages of pulmonary vascular hypertension (grade IV). (Elastic-Van Gieson ×100, reduced by 40 percent.)

temic blood flow ratio (Qp:Qs) was 1.5:1; the pulmonary to systemic vascular resistance ratio (Rp:Rs) was 0.3:1.

He underwent a Mustard operation, performed with use of a Dacron® baffle, at age 13 months (weight 14 lb, 10 oz). During the postoperative course, he required prolonged respiratory assistance. He was discharged from the hospital without arrhythmias or signs of heart failure on the 21st postoperative day. Administration of digitalis was discontinued and he apparently did well for the next several months; hematocrit remained at 40 percent. Seven months postoperatively, he presented with cardiomegaly, hepatomegaly and bilateral pedal edema. In spite of vigorous anticongestive measures during several hospital admissions, there was no improvement in his condition. Progressive cardiomegaly and signs of "right" ventricular failure persisted in the absence of pulmonary congestion. At age 28 months, 15 months after the Mustard procedure, he was readmitted for a fourth cardiac catheterization. The electrocardiogram recorded at this time revealed more prominent posterior forces by comparison with the preoperative tracing, thus suggesting the presence of left ventricular hypertrophy in addition to the right ventricular hypertrophy (Fig. 2). The systemic venous and "right" atrial pressures were greatly increased; there was no pressure gradient between the superior vena cava and the right atrium. The pressure in the left ventricle ("pulmonary ventricle") was

increased to 125/3–18 mm Hg. During the procedure, bradycardia associated with gasping respirations suddenly developed and the patient died despite vigorous attempts at resuscitation.

Autopsy Findings

Gross: The heart and lungs together weighed 550 g (normal weight approximately 300 g). The great arteries were transposed with the aorta anterior and the pulmonary artery posterior (dextrotransposition). The inferior and superior venae cavae entered the anatomic right atrium with no obstruction or malformation. In place of the atrial septum there was a Dacron patch, which was intact and not obstructing any of the vessels emptying into the atria. The anatomic right (systemic) ventricle measured 5 mm in thickness. The anatomic left (pulmonary) ventricle measured 1.1 cm in thickness and was severely dilated and hypertrophied. There were no endocardial, valvular or ventricular septal abnormalities. The ductus arteriosus was closed. The lungs were firm and hypocrepitant with patchy areas of apparent edema, hemorrhage and atelectasis.

Microscopy of lungs: There was marked medial hypertrophy of arterioles and muscular arteries, with cellular and acellular intimal proliferation (Fig. 3 and 4). Several "plexiform" lesions were also found (Fig. 5). These changes were of grades II to IV, according to the classification of Heath and Edwards.[6]

Discussion

The early onset of pulmonary vascular disease in patients with transposition of the great arteries has been well documented.[7–10] Most frequently, pulmonary vascular disease has been noted in patients with an associated large ventricular septal defect. However, various degrees of pulmonary vascular disease have also been reported by Ferencz[8] in infants with transposition of the great arteries and intact ventricular septum. Most of these infants were less than 6 months old and did not have the benefit of atrial septostomy.

With the introduction of balloon atrial septostomy by Rashkind and Miller,[11] the previously dismal prognosis for these patients has changed considerably.[12] More than 80 percent of infants with transposition of the great arteries and intact ventricular septum now survive the first year of life.[13] These infants seem to be the best candidates for correction by the Mustard technique since they do not require repair of additional associated lesions such as ventricular septal defect or pulmonary stenosis. In contrast to patients with ventricular septal defect, patients with an intact ventricular septum usually do not have associated significant pulmonary vascular disease.[4,14]

Reported cases of pulmonary vascular disease after Mustard procedure: Although the immediate postoperative results in patients with transposition of the great arteries with intact ventricular septum are generally good, late complications such as dysrhythmias, vena caval obstruction, tricuspid insufficiency and pulmonary venous obstruction have been described.[2–5] Postoperative development of progressive pulmonary vascular disease in the absence of pulmonary venous obstruction in patients with intact ventricular septum appears to be rare. Viles et al.,[10] in their report on the spectrum of pulmonary vascular disease in transposition of the great arteries, noted a patient, aged 3 2/12 years, who died from progressive pulmonary hypertension 6 1/2 months after a Mustard procedure. This patient had a left ventricular pressure of 40/0 mm Hg before operation and 6 months later manifested signs of congestive heart failure and peripheral edema. Cardiac catheterization revealed pulmonary arterial pressure at systemic levels with severe arterial desaturation and no intracardiac shunts. The patient died 2 weeks later. Although the pulmonary venous pressure was increased, no gross obstruction of pulmonary venous return by the patch was demonstrated at autopsy. The pulmonary vessels in their patient had marked medial thickening, intimal fibrosis and dilatation, indicating grade IV pulmonary vascular disease.[6] More recently, Mair et al.[15] described 10 late deaths in a group of 54 long-term survivors of a Mustard procedure. In two the cause of death was progressive pulmonary vascular disease; both were patients with intact ventricular septum who had near normal left ventricular or pulmonary arterial pressure preoperatively. We assume that one of these was the patient previously described by Viles et al. from the same institution.

In our case, although left ventricular pressure at systemic levels was detected at age 1 month, at repeat catheterization 1 month later this pressure dropped to moderate levels (56 percent of systemic), suggesting persistence of pulmonary hypertension. However, since the pulmonary artery was not entered in either study, the relative contribution of increased pulmonary blood flow or vascular resistance to the pulmonary hypertension could not be estimated. At the time of the third catheterization, a moderate increase in pulmonary vascular resistance was present, suggesting mild pulmonary vascular disease. The patient did quite well for approximately 6 months postoperatively; then signs of congestive heart failure appeared and persisted despite medical management. The heart failure was due to severe pulmonary hypertension secondary to progressive pulmonary vascular disease. This pulmonary hypertension could not be attributed to pulmonary venous obstruction, as verified at autopsy.

Factors causing postoperative pulmonary vascular disease: The etiology of pulmonary hypertension in infants with transposition of the great arteries with or without a ventricular septal defect has been discussed repeatedly. Increased pulmonary blood flow as well as an increase in the pulmonary "perfusion pressure" in infants with transposition of the great vessels and an intact ventricular septum have been postulated as etiologic factors in the development of pulmonary vascular disease.[8–16] With increased pulmonary blood flow, the resultant increased pulmonary venous pressure in a system in which the right and left heart circulations are parallel might contribute to pulmonary vascular obstructive disease, as seen with mitral stenosis. Burchell[17] sug-

gested that bronchial flow, with its blood at low oxygen tension and pH levels, might effect a locus of resistance vessels in the lungs. The high levels of oxygen content and viscosity in the pulmonary arterial circuit might contribute to the early onset of pulmonary vascular disease. The development of progressive pulmonary vascular disease postoperatively is difficult to explain. With the introduction of the intraatrial baffle at the time of the Mustard procedure, partial or total obstruction of the pulmonary venous ostia may occur. The baffle may also create long-term problems if patch contracture creates obstruction to the pulmonary venous system and leads to pulmonary hypertension.[18] Also, pulmonary microemboli from the patch may contribute to the development of pulmonary vascular disease in the absence of pulmonary venous obstruction.

Certainly the mechanisms responsible for the development of pulmonary vascular disease are not clear and, in the group of patients described by Viles et al.,[10] there was a wide spectrum of changes in the pulmonary vascular bed in patients of similar age who had similar anatomic and physiologic alterations. To explain the individual variability of pulmonary vasoreactivity in general, Blount and Vogel[19] introduced the term "hyperreactor" for patients who react strongly to a specific stimulus and, conversely, "hyporeactor" for patients who react minimally. They postulated that pulmonary vascular disease will develop more readily in hyperreactors than in hyporeactors, regardless of the type of stimulus.

In our patient, the pulmonary vascular changes were severe, as demonstrated by the presence of "plexiform" lesions. Since there was mild pulmonary hypertension preoperatively and lung biopsy was not performed at operation, it is difficult to determine precisely when these changes occurred. That earlier surgery, recommended by many centers, would have prevented the development of permanent pulmonary vascular changes in our patient is speculative.

However, regardless of the causes, the postoperative development of progressive pulmonary vascular disease in some patients with transposition of the great arteries and intact ventricular septum is disturbing. The frequency of this complication is not known, but it may be a factor in late deaths after the Mustard operation.

Acknowledgment

Both operations were performed by Dr. Richard J. Cleveland, now professor and chief of cardiovascular surgery, Tufts University School of Medicine, Boston, Mass.

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Radionuclides and the Patient with Coronary Artery Disease

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The emergence in the past 20 years of nuclear medicine as a distinct diagnostic discipline has been a major clinical advance. The relatively rapid evolution from the small laboratory limited primarily to the study of thyroid disease to the large unit in which radioactive tracers (radionuclides) are utilized to evaluate structure and function of most organ systems has been accelerated by major advances in instrumentation, new radioactive tracers and application of computer techniques. Application of these radionuclide techniques to the study of coronary artery disease has been quite recent, and has in part been limited by the need for a coordinated effort between the cardiologist and the specialist in nuclear medicine. However, realization of the potential usefulness of these techniques has fostered an increasingly productive liaison between the two specialties. The potential advantages of these radionuclides in evaluating patients with cardiovascular disease is twofold: first, they may permit the noninvasive or atraumatic acquisition of data that might otherwise be obtained only at the time of cardiac catheterization; second, and perhaps more important, they may permit the acquisition of physiologic measurements or observations not attainable by more conventional modes of study. Functionally, these techniques can be divided into those that evaluate cardiac performance and those that evaluate coronary blood flow, regional myocardial perfusion and myocardial viability.

Assessment of Cardiac Performance

Radiocardiography: The assessment of cardiac performance with radioactive tracers can be performed in a variety of ways. In all techniques the procedure is virtually noninvasive. The long-term value of these techniques when compared with other noninvasive approaches such as echocardiography has yet to be defined. The simplest approach is the technique of radiocardiography as developed by Donato.[1] After the injection of a radionuclide into either a peripheral or central vein, passage of the radioactive injectate through the central circulation is recorded. The detector used in this technique is a single crystal probe positioned over the precordium. The recording of the precordial transit or radiocardiogram appears as two distinct and continuous peaks corresponding to passage of the injectate through the right and then the left heart chambers. From this initial indicator-dilution curve and subsequent blood volume determination, it is possible to measure cardiac output, pulmonary transit time and pulmonary blood volume. If the precordial transit is recorded at rapid speeds with a sufficiently sensitive instrument, high frequency oscillations corresponding to each heartbeat are noted during the downslope of the left ventricular portion of the curve. It has been proposed that the magnitude of these oscillations, after background correction, can be related to left ventricular ejection fraction.[2] The single crystal probe is the simplest and least expensive detector available. It is relatively small and generally mobile and hence can be moved to the bedside of the acutely ill patient. However, the data are obtained in the form of a single curve, and there is no assurance as to the anatomic structure being sampled by the probe.

Radionuclide angiocardiogram: With the use of the more sophisticated and complex scintillation camera, the passage of the same injectate through the heart may be visualized as a radionuclide angiocardiogram and assessed both qualitatively and quantitatively. As the radioactivity passes through each cardiac chamber it is sequentially recorded either on a video storage system for subsequent analysis or directly on line with a rapid sequence photographic camera. Visual anatomic definition of each cardiac chamber is obtained. On a purely qualitative basis, this record can be utilized to assess relative chamber and great vessel size and to detect intracardiac shunts or various congenital and acquired anatomic abnormalities.[3] The left ventricular phase of the radionuclide angiocardiogram can be analyzed much like the more familiar contrast angiogram, and left ventricular end-diastolic volume can readily be de-

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termined.[4] The output of the scintillation camera is easily interfaced with a computer system. Individual regions of interest can then be studied quantitatively and individual indicator-dilution curves determined for each cardiac chamber or region. The same system can then be applied to a quantitative hemodynamic assessment of patients with heart disease.[5–7]

By introducing a physiologic signal into the system—that is, electrocardiographic gating—data are obtained only during selected portions of the cardiac cycle. When these data are summed over several cycles, mean cardiac scintiphotographs are obtained for only the selected portion of each heartbeat. When this procedure is applied to end-systole and end-diastole, pertinent information on ventricular volumes and left ventricular ejection fraction are obtained.[8] The data can be determined from the chamber contours either by applying formulas developed for the determination of left ventricular volumes by contrast angiography or by quantifying radioactivity within specifically identified regions corresponding to the left ventricular chamber. The use of electrocardiographic gating for evaluation of chamber volumes, ejection fraction and regional left ventricular wall motion can be applied as well to the static blood pool image. In this instance, a radionuclide that remains within the intravascular space must be used, and summed data are obtained over 200 to 300 cardiac cycles.[9–11]

Available radionuclides: The radionuclide used most frequently in assessing cardiac performance is technetium-99m (^{99m}Tc). When only the initial cardiac transit is evaluated, the radioactive tracer is usually injected as the ion, pertechnetate-99m. When analysis of blood pool images is required, ^{99m}Tc is bound to human serum albumin, thus becoming an intravascular marker. This radionuclide is available in every clinical nuclear medicine facility, is inexpensive and has ideal imaging characteristics. Indium-113m is another readily available inexpensive radionuclide that has been used for single probe radiocardiography. Once injected, this radionuclide immediately binds to serum transferrin and thus remains within the intravascular space.

Advantages and drawbacks: Several studies have now reported good correlation between these data and independent measurement of left ventricular performance by contrast angiography. These techniques are now applicable to the study of the patient with myocardial infarction.[8,12] Because they are noninvasive they can be frequently repeated, and can function as both screening tests and follow-up procedures. Their major disadvantage is the expense of the equipment. Most scintillation cameras are not sufficiently mobile to be transported from one unit to another and, hence, dedicated equipment is required in acute care areas.

Measurement of Coronary Blood Flow

For many years total coronary blood flow has been evaluated after the intracoronary or left ventricular injection of radioactive inert gases (xenon-133, krypton-85), with recording and analysis of precordial washout curves according to the Kety-Schmidt method.[13,14] These techniques permit measurement of mean total coronary blood flow but give no information regarding the more critical questions of flow and perfusion to individual myocardial regions and the interrelation among normal and abnormal myocardial zones in the atherosclerotic heart. Consequently, these methods have been of limited diagnostic value. They do have a place in the investigative laboratory where the assessment of acute changes in total coronary blood flow provides valuable physiologic data. An example of this use would be the evaluation of pharmacologic interventions.

Total coronary blood flow can be evaluated noninvasively by employing precordial coincidence counting of the positron emissions of intravenously administered rubidium-84.[15] As with the previously cited methods, total rather than regional coronary blood flow is measured, and the same limitations apply.

Assessment of Regional Myocardial Perfusion

In the clinical and investigative study of coronary artery disease, an assessment of blood flow and perfusion to individual regions of the myocardium is most significant. Regional myocardial perfusion can be evaluated with radionuclides both noninvasively, after intravenous injection, and directly, after intracoronary injection at the time of coronary arteriography. Whatever the mode of tracer administration, the data obtained are unique and present a physiologic indicator of capillary perfusion, myocardial blood flow and myocardial viability. Recent advances have been focused on identification of regions of infarction as well as zones of transiently ischemic myocardium. The intravenously administered radionuclides utilized with most success have been potassium-43 (^{43}K),[16] cesium-129 (^{129}Cs)[17] and, more recently, rubidium-81 (^{81}Rb).[18] Recently ^{13}N ammonia has also been studied,[19,20] but this radionuclide is limited in use by its extremely short half-life and dependence on cyclotron production.

Intravenous radionuclide injection: These agents concentrate in myocardium in proportion to blood flow, tissue viability and the size of the regional cation pool. Infarcted regions appear as "cold spots" of decreased radioactivity concentration on the myocardial image obtained with either the rectilinear scanner or the scintillation camera. In patients with severe arterial stenosis and angina pectoris rather than myocardial infarction, comparable defects of decreased radioactive tracer concentration are not detected when patients are studied at rest. However, when the radionuclide is administered during a circulatory stress such as exercise, relative decreases in regional tracer concentration become apparent and transiently ischemic myocardium can be visualized.[16,21] The radionuclide is administered during stress and distributes within the myocardium during that pathophysiologic circumstance. Myocardial im-

ages are obtained during the subsequent rest period when the patient's condition is stable and has clinically and hemodynamically returned to a base-line state. Radionuclides of potassium and rubidium are more suited for this type of study than are those of cesium because their more rapid myocardial extraction allows relatively complete myocardial distribution during the stress state.

Zones of relative hypoperfusion or ischemia detected during stress imaging with ^{43}K have correlated with the regional location of vascular beds supplied by stenotic major coronary arteries in patients undergoing coronary arteriography. The technique of ^{43}K myocardial imaging during rest and exercise has been shown to be of value in assessing the results of aortocoronary bypass surgery[22] and in evaluating a group of patients with false positive electrocardiographic responses to maximal treadmill exercise.[23] In an initial assessment this approach seems capable of answering questions regarding infarct size, differentiation of ischemia from infarction and, most important, definition of the functional significance of a given arterial stenosis. Because the approach is noninvasive it also permits longitudinal evaluation of the patient with coronary artery disease. All radionuclides currently available for this approach are cyclotron-produced and also have relatively short half-lives. This factor and their high cost currently limit their widespread application

Intracoronary radionuclide injection: The two major approaches to the study of regional myocardial perfusion at the time of coronary arteriography have involved the intracoronary administration of xenon-133 (^{133}Xe)[24] and radioactive-labeled albumin macroaggregates (MAA).[25,26] With the ^{133}Xe technique, the detector employed is a computerized scintillation camera system. Multiple right and left ventricular regional washout curves are obtained in several projections; hence, the problems encountered with the use of ^{133}Xe and a simple precordial washout curve are eliminated. With the MAA technique, radioactive particles are transiently embolized within the coronary microcirculation, and scintiphotographs that can be evaluated either qualitatively or quantitatively are later obtained. Because the tracer is placed directly in the vascular bed to be evaluated, visualization and resolution are optimal and background activity is minimal. The safety of these procedures has been established by several groups. Repeated study is limited by the mode of administration. Most studies have been performed without imposed circulatory stress. Initial studies with MAA during the resting state have already proved capable of defining viable and nonviable myocardium, thus adding to the specificity of selection of patients for revascularization procedures.[26] Recent application of these techniques during the stress of either atrial pacing[27] or intracoronary administration of contrast medium[28,29] has allowed definition of transiently ischemic regions as well as the more readily defined zones of infarction. The addition of circulatory stress to these procedures should greatly enhance their utility.

Visualization of acute myocardial infarction: A final cardiac application of radioactive tracer techniques is the visualization of acutely infarcted myocardium with the use of radionuclides that are selectively incorporated into the acute infarct. In this technique the acute infarct is viewed as an area of increased radioactivity or "hot spot." Initial attempts with this approach were unsuccessful because of undesirable physical and biologic properties of the chosen radionuclides. Recent preliminary studies with technetium-99m-tetracycline[30,31] and technetium-99m-pyrophosphate[32,33] have yielded more encouraging results. Dual radionuclide studies with both "hot spot" and "cold spot" agents may offer a new approach to the quantitative assessment of infarct size and periinfarction ischemia.

Clinical Implications

Radionuclide techniques now offer the possibility of evaluating the patient with coronary artery disease in terms of major areas of clinical concern: ventricular performance, coronary blood flow and regional perfusion. The techniques are for the most part noninvasive, allowing repeated use and sequential and longitudinal evaluation. Their clinical utility in small groups of patients with overt disease has been established. The next decade should see a wider longitudinal study involving the identification of the high-risk patient with covert coronary artery disease, the functional assessment of the patient with angina pectoris or myocardial infarction, and the functional evaluation of medical and surgical therapy. It is not inconceivable to expect the same patient to be studied and evaluated during various phases of his disease, with radionuclide techniques furnishing objective guidelines as to therapy and prognosis. Neither the ideal radionuclide for all types of study nor the ideal radiation detector is yet available. One would expect that their development is just a matter of time.

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SURGICAL CORRECTION OF DOUBLE OUTLET RIGHT VENTRICLE

I read with interest the recent article by Agarwala et al.[1] concerning the surgical correction of Taussig-Bing variant. I congratulate them on their success in this very difficult operation and quite agree with their opinion that pulmonary stenosis is a rarely associated lesion in the Taussig-Bing malformation. However, their statement that "an identical case with a similar type of surgical correction has not previously been reported" is misleading.

In April 1967, Patrick and McGoon[2] successfully operated on an 8 year old girl with a variant of the Taussig-Bing complex. They reported that in their case the aorta originated anterior to the outflow tract of the right ventricle and the pulmonary artery originated directly behind. The operation was performed inside the right ventricle; a long oval patch of knitted Teflon® was sutured to the left and anterior of the pulmonary valvular ring connecting the ventricular septal defect and aortic ostium so that blood from the left ventricle could be transmitted to the aorta as in the case of Agarwala et al.

In September 1969, I[3] successfully operated on a 7 year old girl with typical Taussig-Bing malformation without pulmonary stenosis. A tunnel of knitted Teflon was created to connect directly the ventricular septal defect and aortic ostium after resection of the distal conal septum, which was separating the infundibula.

To my knowledge, these are the previously reported cases of Taussig-Bing malformation or its variant operated upon successfully with the intraventricular rerouting technique, which is almost identical to the method described by Agarwala et al.

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REPLY

It was certainly an omission for us to have neglected to include Dr. Kawashima's case report of intraventricular rerouting for correction of Taussig-Bing anomaly, as well as the earlier report by Patrick and McGoon in which a similar technique was used. We had been focusing on the unusual anatomic variant in our case, the presence of severe infundibular pulmonary stenosis. This was the aspect that we felt made the case worth reporting and made the surgical repair so difficult. Neither of the cases cited by Kawashima had associated pulmonary stenosis.

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RIGHT VENTRICULAR INFARCTION

Cohn et al.[1] have significantly extended the understanding of hypotension in acute myocardial infarction by drawing attention to the role of right ventricular infarction. An earlier report by the late B. W. Lassers and his associates[2] recognized dominant right ventricular failure in patients with acute inferior wall myocardial infarction and suggested that right ventricular damage plays a role. Observations on the milder forms of the syndrome, including oliguria without hypotension, together with therapeutic suggestions, were recently published.[3]

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REPLY

My colleagues and I appreciate the comments by Dr. Schwartz and the reference to his recent publication, which we had not seen. Although the diagnosis can be suspected clinically, as in Dr. Schwartz's case reports, we would warn against making the assumption of predominant right ventricular failure without actual measurement of left ventricular filling pressure. Indeed, a normal or near normal left ventricular filling pressure in the presence of systemic venous hypertension is probably a contraindication to the diuretic therapy that Schwartz used with apparent success in several of his patients. This syndrome therefore provides a good example of why bedside monitoring of left ventricular function is so vital in making rational therapeutic decisions in patients with a complicated course after acute myocardial infarction.

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Convenient, easy-to-use 28-day Hygroton PAK costs no more than a regular monthly supply of Hygroton tablets.[2]

1. Finnerty, F. A., Jr.: Am. Fam. Physician 7:99, 1973.
2. Based on American Druggist Blue Book (1974) prices.

ALSO AVAILABLE:

Hygroton® 100 mg. PAK
(chlorthalidone)

USV PHARMACEUTICALS

USV PHARMACEUTICAL MFG. CORP.
Manati, P.R. 00701

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone; routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May be additive or potentiative of the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Usage in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in cord blood and breast milk. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; single-dose blister packs, boxes of 500; PAKS of 28 tablets, boxes of 6.

EKG SOL®

the original electrode cream with many imitators...but no rivals!

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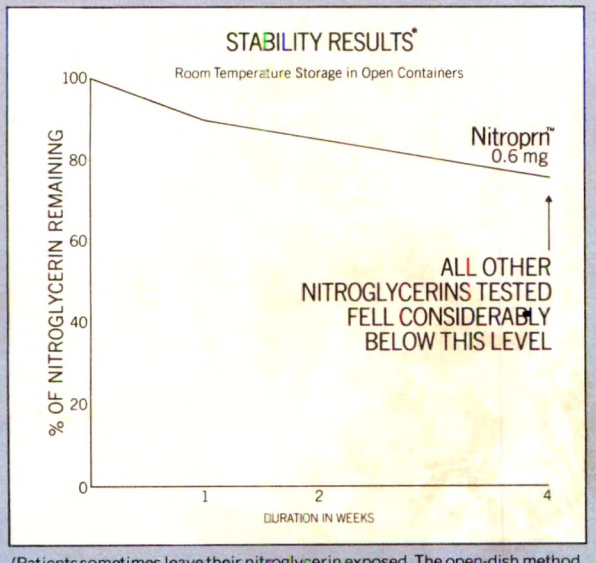

(Patients sometimes leave their nitroglycerin exposed. The open-dish method, a most demanding stability test, shows that Nitroprn retains its potency even under extreme exposure, thus protecting even careless patients.)

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*Methods used: The semi-automated Content Uniformity Assay based on the procedure of Fusari, S.: J. Pharm. Sci. 62:122 (1973), with modifications by the Applied Analytical Research Laboratories of Warner-Lambert Company. Data on file, Warner-Lambert Research Institute.

On Reliability and a Pound of Flesh

The life's blood of an electrocardiograph is the chart that flows through it.

Assurance that the recording is totally reliable depends, in part, on the quality of the chart itself.

Charts, as provided by the instrument maker, afford this assurance to a maxima ... because they are designed as an integral part of the instrument.

Charts, as provided by others, are imitations at best. They may save a few pennies, but not without risk of shedding a "drop of reliability".

This message was prepared in the interest of better instrument performance by ...

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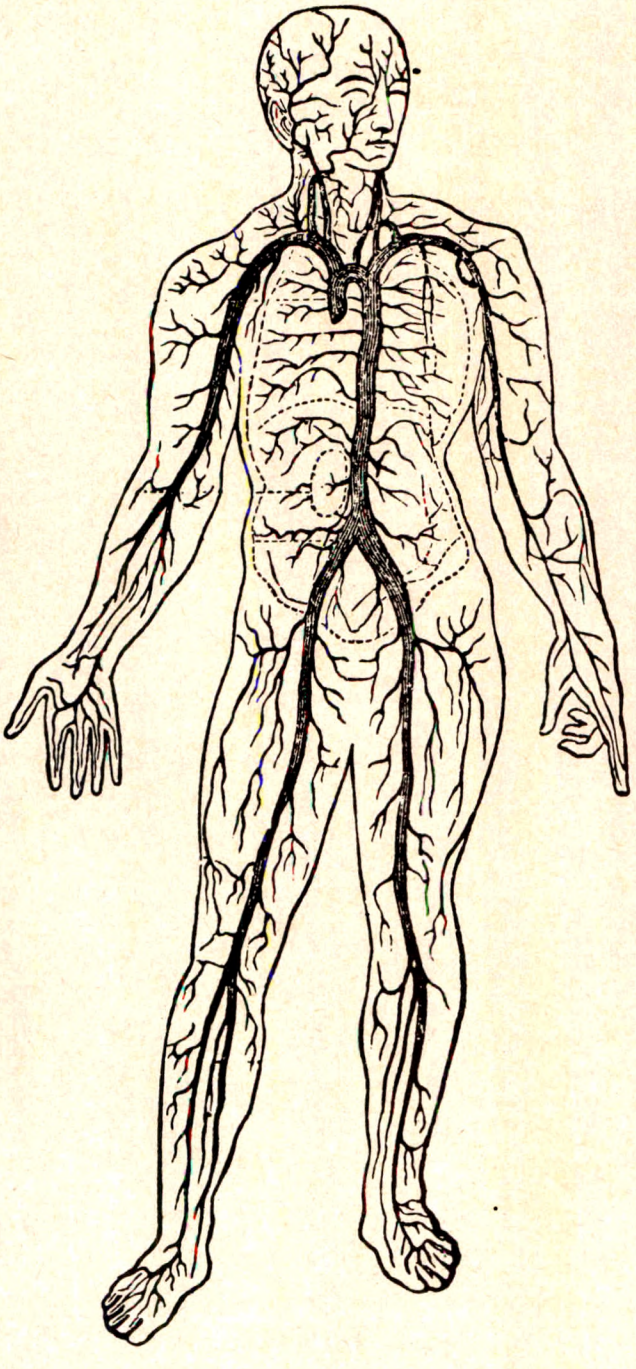


INTROPIN®
(dopamine HCl)

Intropin usually turns on:

Increased perfusion of vital organs

Multiclinic trials have demonstrated that Intropin provides adequate perfusion of vital organs. This is based upon a number of clinical parameters including an increase in urine flow which appears to be one of the better diagnostic signs of increased vital organ perfusion.

Increased urine output

Intropin significantly increases urine flow. This is in contrast to most other sympathomimetic amines, which usually cause little or no significant increase in urine output.

This increased urine output is due to increases in glomerular filtration rate and renal blood flow and is accompanied by increased sodium excretion. Intropin may also increase urine flow in patients whose urine output is within normal limits and may promote diuresis usually with no decrease in osmolality.

At doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage.

Increased cardiac output

Intropin acts predominantly on the beta receptors of the heart to substantially increase contractility, stroke volume and cardiac output, as confirmed by invasive technique.

Increased blood pressure

Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of Intropin. Prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer Intropin as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

A new drug for low cardiac output and hypoperfusion in the shock syndrome.

Intropin usually will not turn on:

A substantial increase in tachyarrhythmias

One investigator reported less than a 3% incidence of tachyarrhythmias in clinical trials of 270 patients. The tachyarrhythmias which occurred were easily managed.

Excessive myocardial oxygen consumption

Intropin produces less increase in myocardial oxygen consumption than isoproterenol. During administration of Intropin, the myocardial oxygen supply/demand ratio has usually remained stable. Intropin appears to meet additional myocardial oxygen requirements by increasing coronary flow.

Increased total peripheral resistance

Administration of Intropin, at low and intermediate dosages, generally does not increase total peripheral vascular resistance. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases.

Intropin is indicated for the correction of hemodynamic imbalances in the shock syndrome due to: myocardial infarction, trauma, endotoxic septicemia, open heart surgery, renal failure and chronic cardiac decompensation as in congestive failure.

The pharmacological actions of Intropin appear to differ significantly from other catecholamines. Over 6 years of clinical trials at more than 30 teaching hospitals have shown that Intropin can increase cardiac output, vital organ perfusion and renal flow with a low incidence of undesirable effects.

Patients most likely to respond adequately to Intropin are those in whom urine flow, myocardial function and blood pressure have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and Intropin, the better the prognosis. Survival rates are considerably improved when Intropin therapy is initiated within 4 hours of onset of symptoms.

As with all potent drugs, Intropin must be administered under close medical supervision. It is administered only by I.V. drip after dilution in a suitable I.V. solution.

Serious undesirable effects seldom occur

In multiclinic studies, adverse reactions necessitated discontinuation of Intropin therapy in only 11 (2%) of 526 patients.

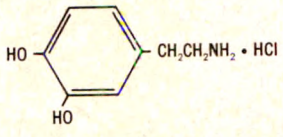
Before prescribing, see complete product information on the following page.

ARNAR-STONE LABORATORIES, INC.

INTROPIN® (dopamine HCl)

5 ml. AMPUL / FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3,4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects or specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do NOT add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

December 1974

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Although in clinical trials inadvertent subcutaneous infiltration did not produce any evidence of necrosis, the usual precautions should be taken to avoid extravasation.

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

ARNAR-STONE LABORATORIES, INC.
A Subsidiary of American Hospital Supply Corporation
Mount Prospect, Illinois 60056

ASL-1-75-4080

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CPR represents a system of delivery of health care in the field of cardiac rehabilitation which:

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A CPR Center can be fully-designed and equipped with sophisticated testing and monitoring equipment, staffed by nurses trained in exercise physiology and cardiac rehabilitation, and operational within your hospital in less than 90 days.

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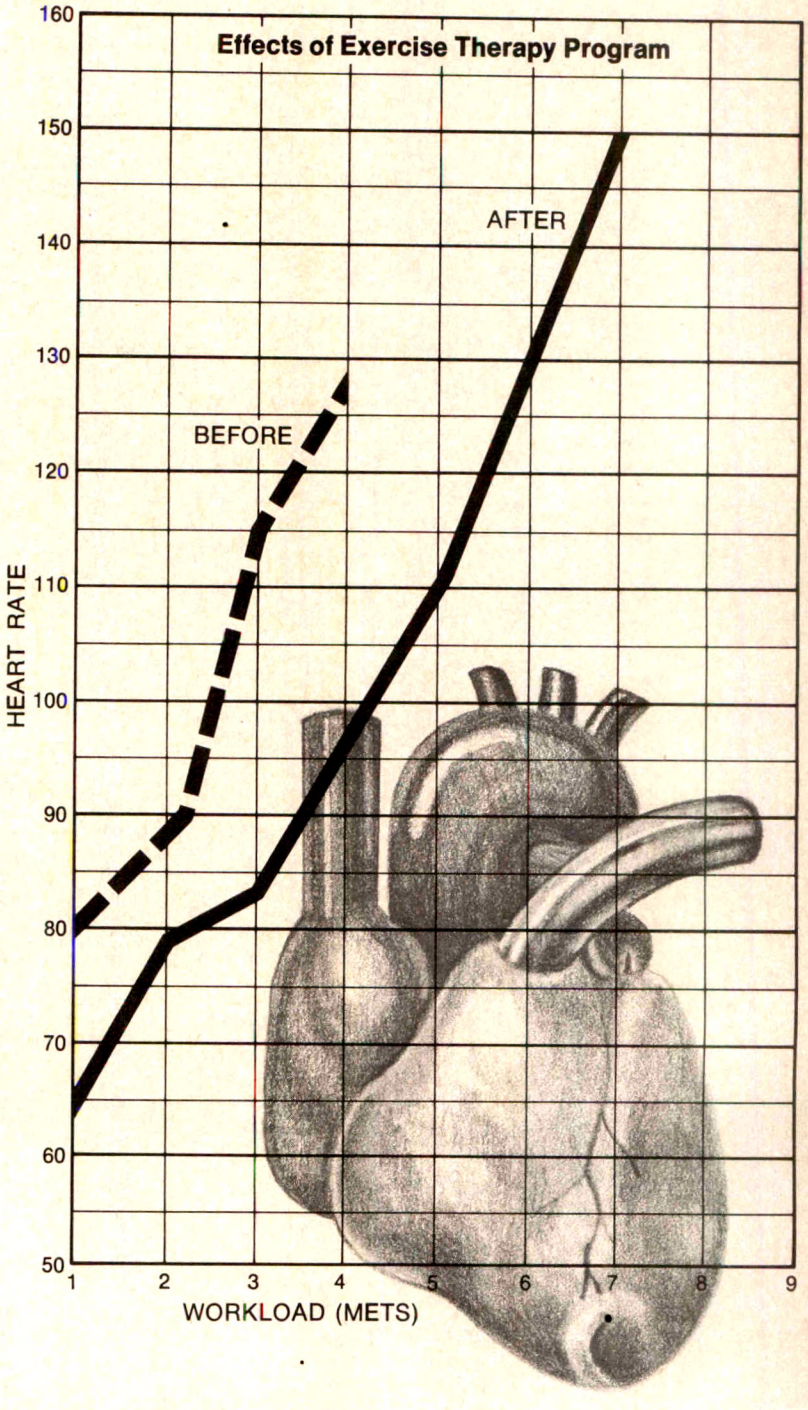

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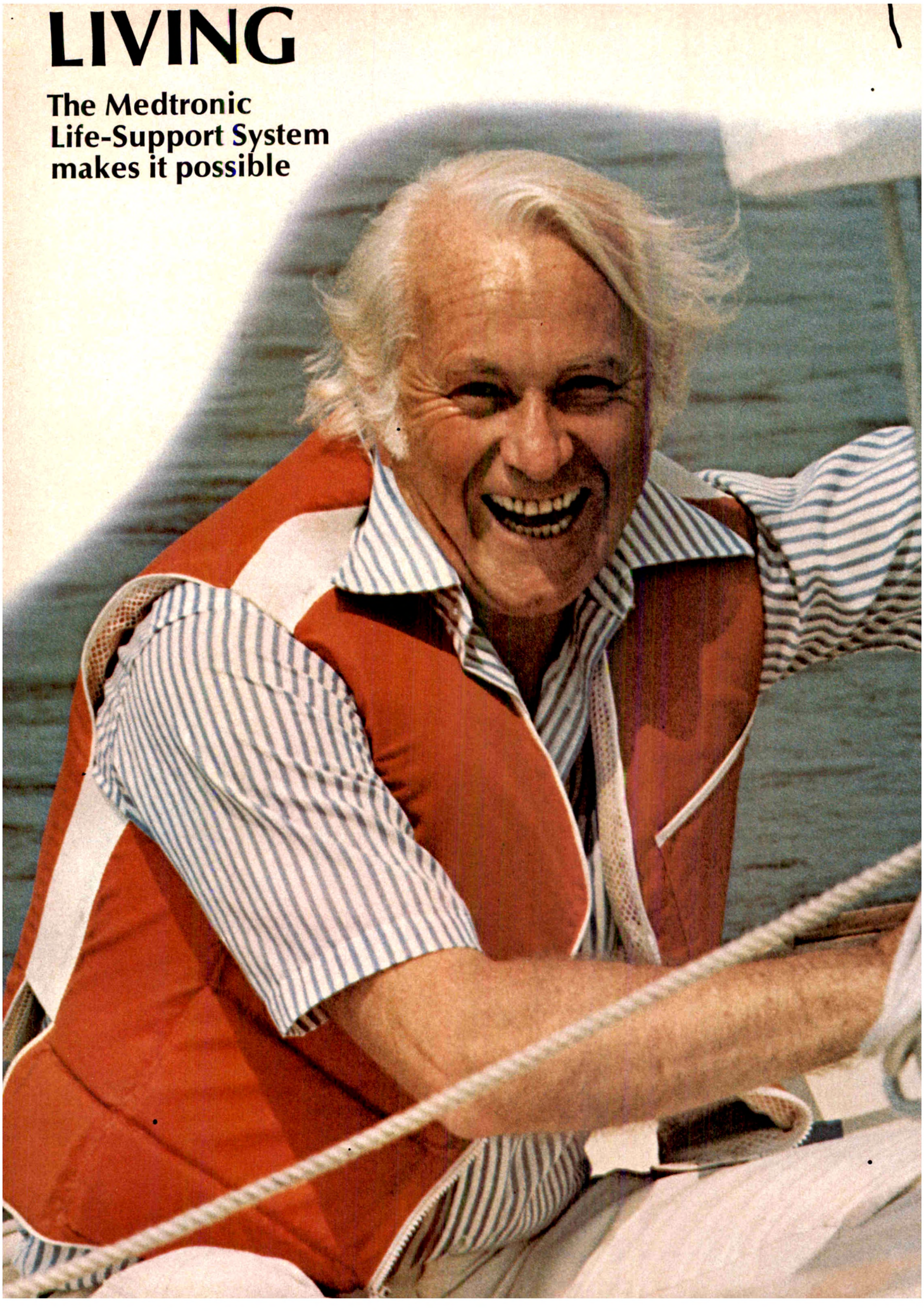
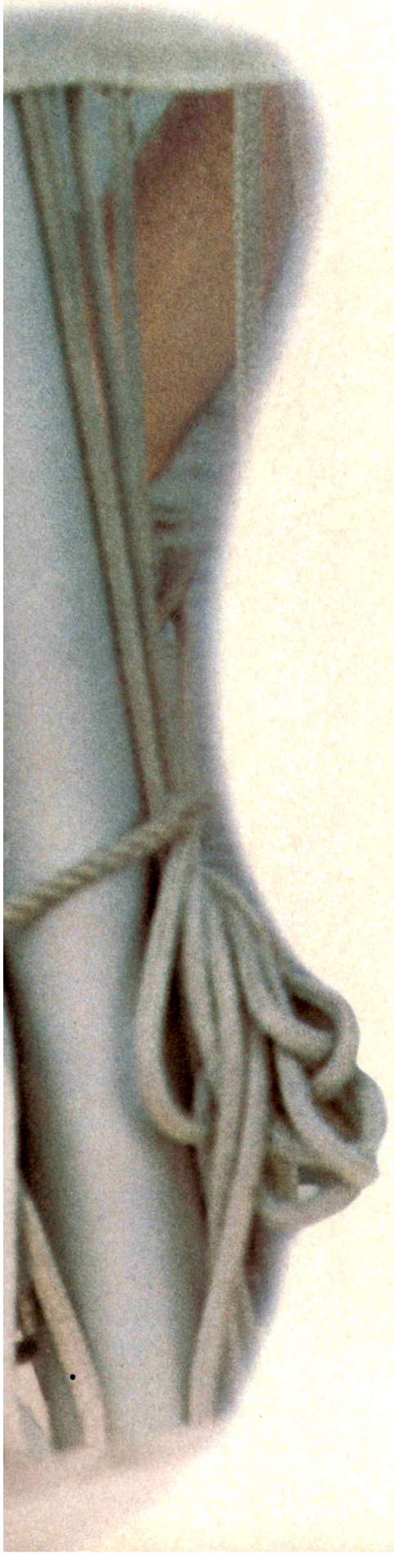
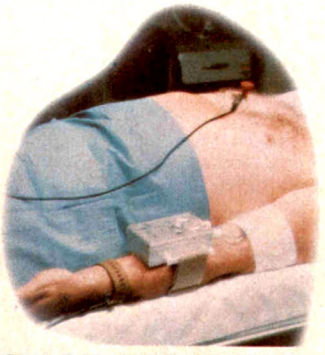




A coordinated system providing continuous control of the pacemaker patient from pre-implant care to post-implant follow-up



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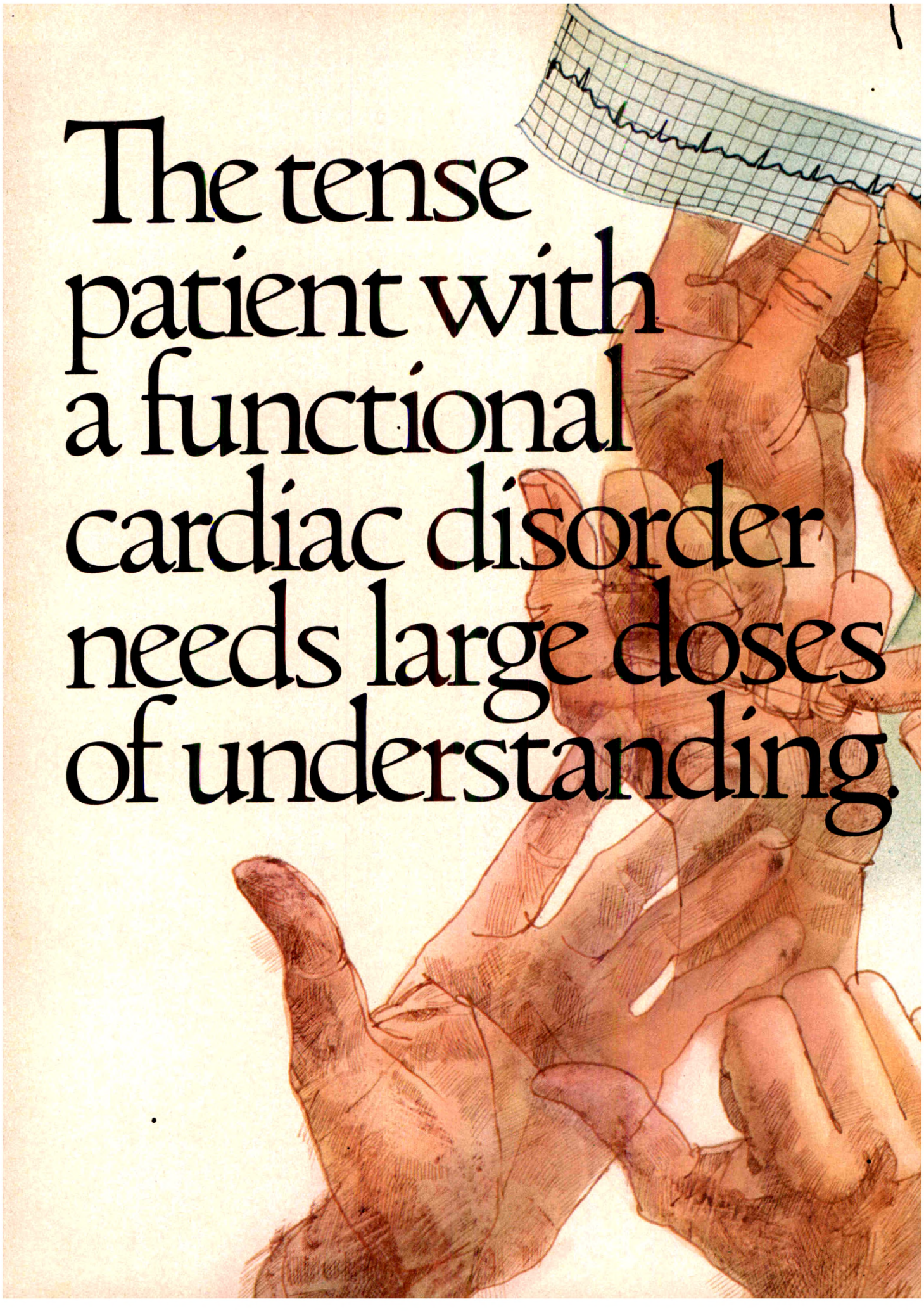
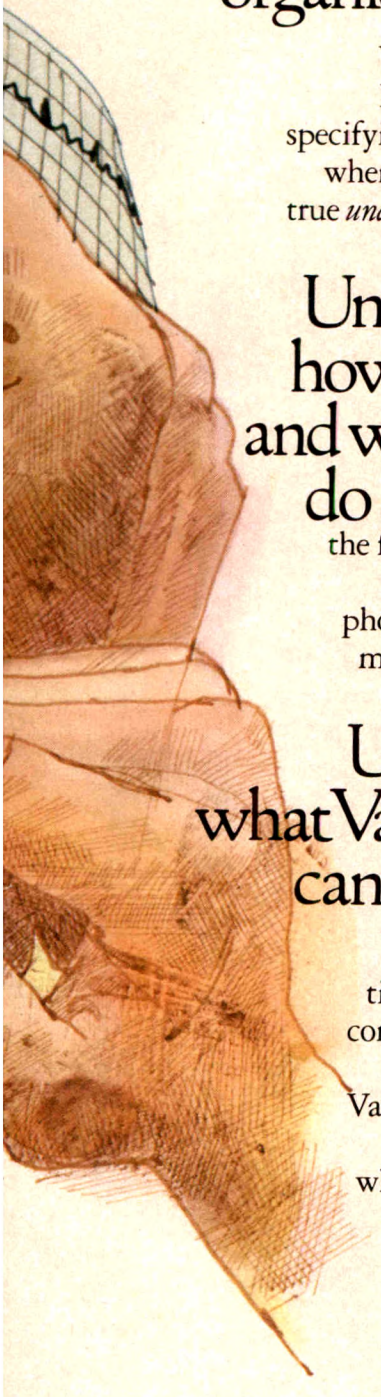
Medtronic representatives are strategically located throughout the world. For more complete product information contact the representative nearest you.

Medtronic
THE PACEMAKER
IN PACEMAKING


The tense
patient with
a functional
cardiac disorder
needs large doses
of understanding.



Understanding that there is nothing organically wrong

He may have been living with chest pains and anxiety about his heart for months, or even years. He finally gets up the courage to see you about it, maybe because a close friend just died of a heart attack.

You do a full work-up. No organic problem. What next?

Reassurance, of course. Immediate. Emphatic. Detailed in terms of specifying that he doesn't have any of the diseases the average person thinks of when he has chest pains. The kind of reassurance that hopefully results in true *understanding* that there is nothing physically wrong.

Understanding how you can help and what he must do for himself

The patient may think "What a relief," and walk out of the office feeling like a million dollars. But in case the anxiety is too deep for that, he needs more understanding. Understanding that his pain may remain for a while and that *he* must really accept the fact that it's not his heart, but his anxiety that's causing the symptoms.

He also needs to understand that you're there — as close as his phone — if he needs you. And that he can always set up another appointment to talk to you again.

Understanding what Valium (diazepam) can do when it's indicated

If the patient is very tense and anxious, he may be unable to benefit fully from the understanding you provide. Valium (diazepam) *t.i.d.* for a week or two may be helpful as an adjunct. It's effective, prompt and relatively safe. Yes, there are precautions, and adverse reactions can occur. Have you read through the Valium complete product information lately?

The patient's understanding will be complete if you discuss his Valium therapy with him in some detail, including what you believe it can and can't do for him, how much he should take, for how long, and when you expect to be able to stop the medication.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg scored tablets

Prescribe it with understanding for the overly tense patient with functional cardiac symptoms

ROCHE

For a summary of complete product information, see following page

Prescribe it with understanding for the overly tense patient with functional cardiac symptoms

Valium® (diazepam)

2-mg, 5-mg, 10-mg scored tablets

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 100; Prescription Paks of 50, available singly and in trays of 10.

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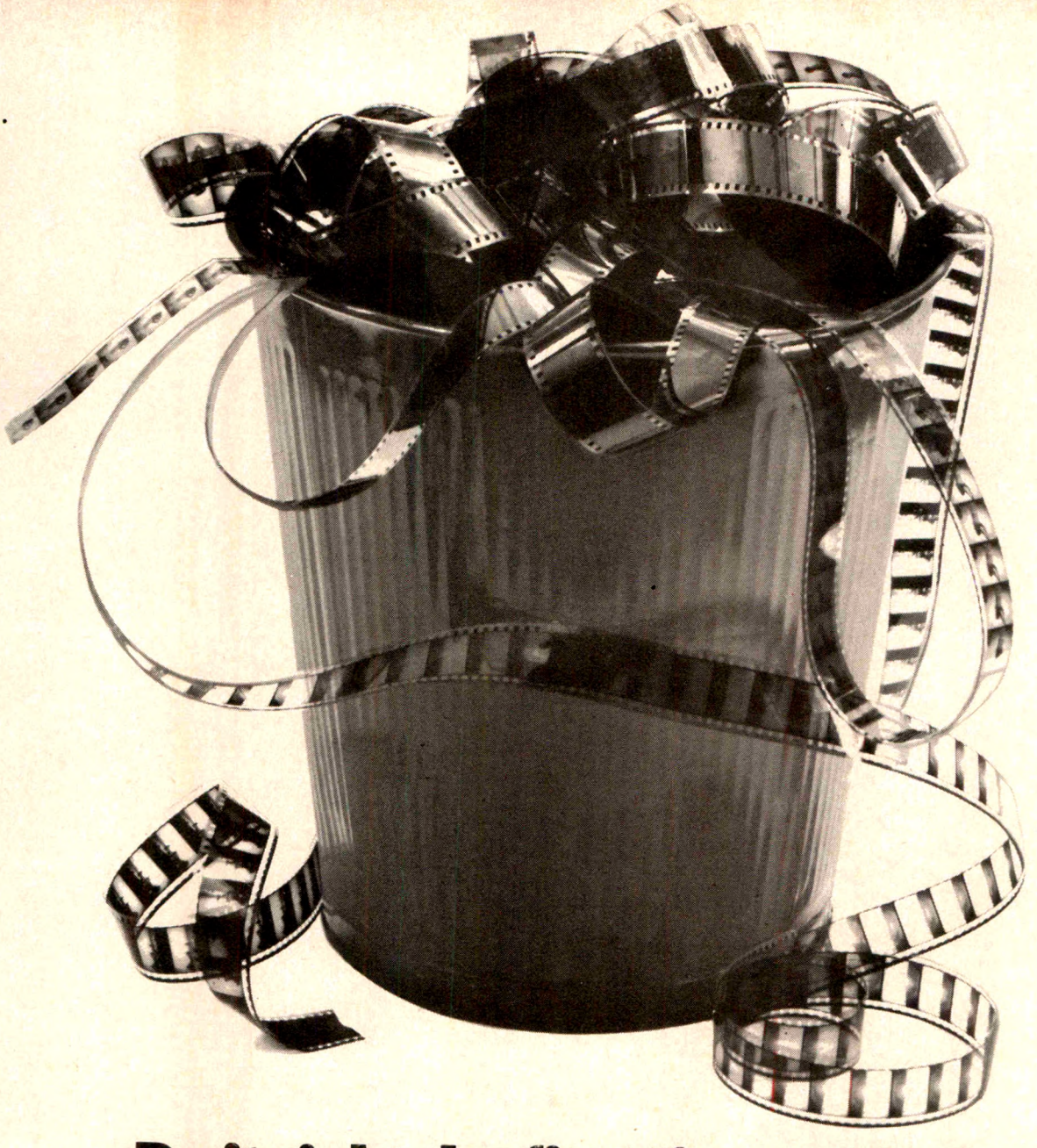

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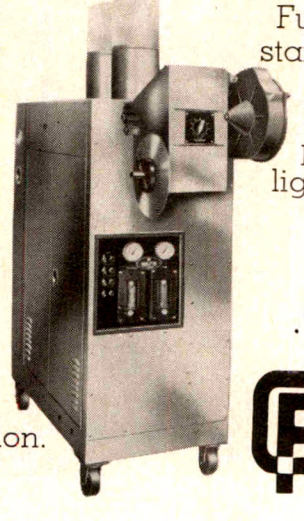

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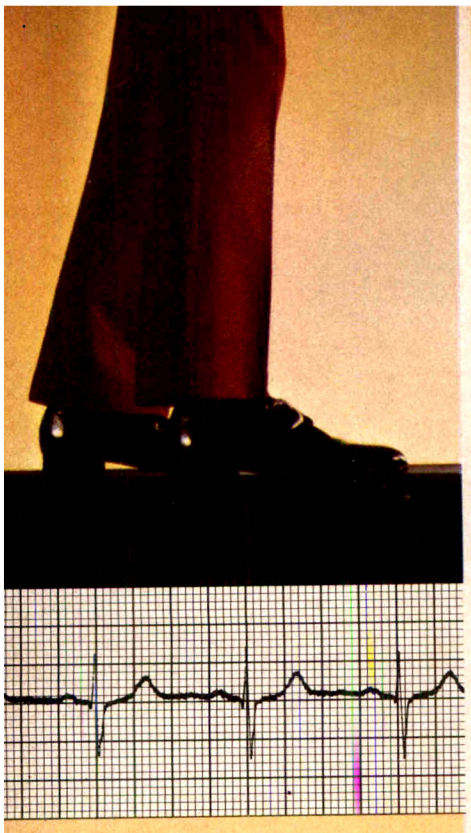
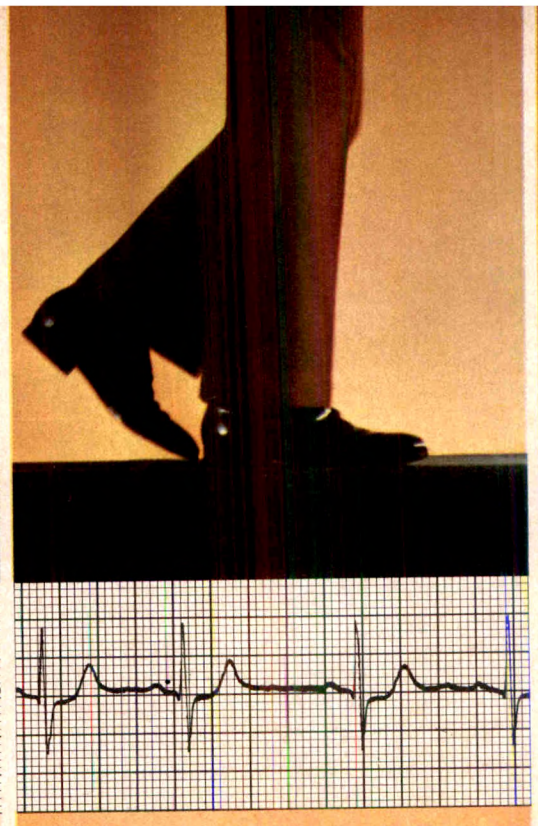
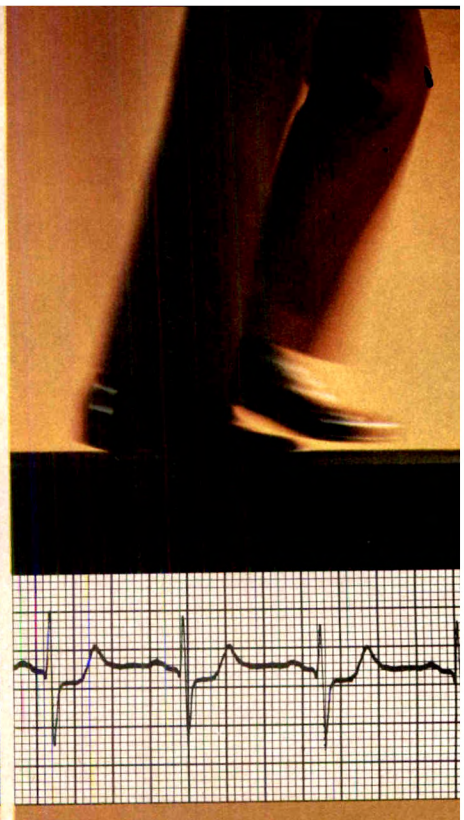


Standing, at rest, V-5, HR-74. American's Stress Test Electrode supplies immediate base line stability. Testing with a narrow, drift free base line can begin as soon as the self-adhering, silver/silver chloride electrodes have been applied to the patient and connections made to your monitoring equipment.



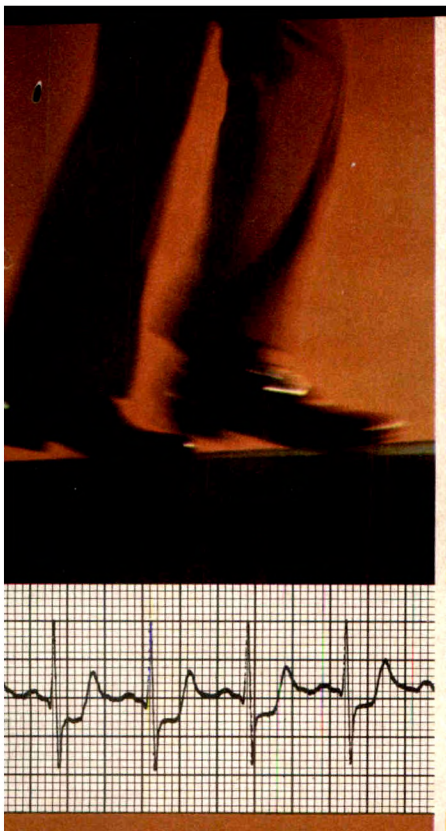
4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and impregnated foam pad which is slightly oversize to assure positive, continuous pressure at the electrode-skin surface. The results: immediate onset and virtual elimination of base line instability and motion artifact.

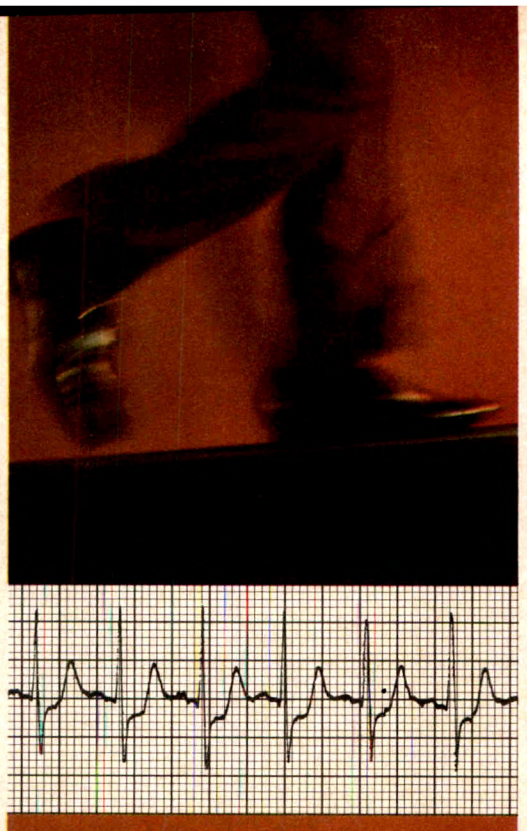


4th Minute at 3 mph (8th minute of test), 0% Grade, V-5, HR-83. (The patient's ECG indicates 1 mm of S-depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interferenc that might otherwise mask small amounts of S-T depression.

Finally.

An electrode/cable system specifically designed for stress testing.

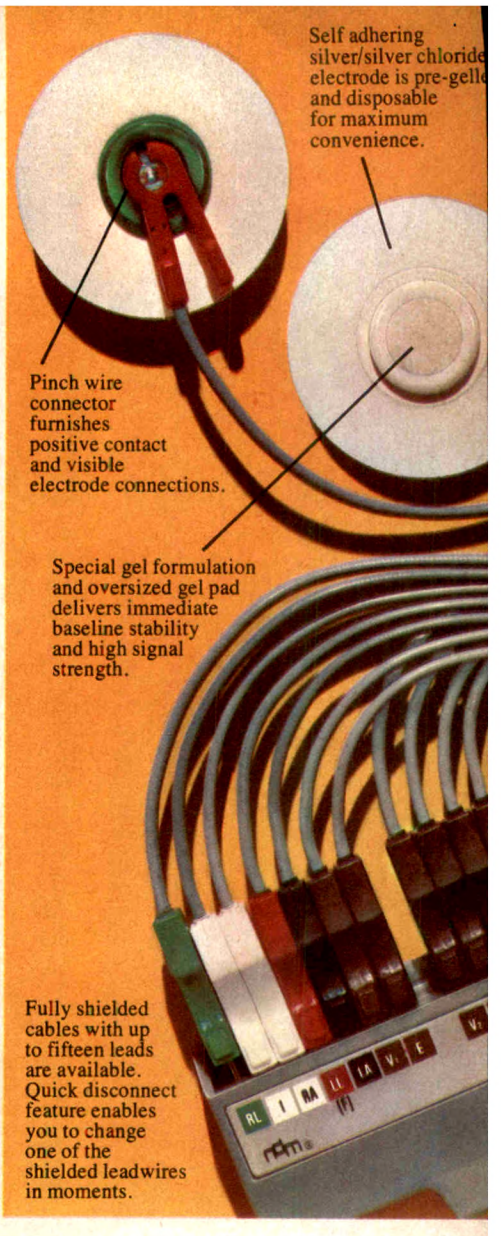




Minute at 3 mph (12th minute
est), 5% Grade, V-5, HR-117.
T depression increases to 2.5 mm.)
en at high work loads, the Ameri-
Stress Test Electrode and fully
elded cable system delivers a stable
e line and noise-free signal.

4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.)
Long test procedures* seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

* Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's new Stress Test Electrode and fully shielded cable system.

If you've been diagnosing from stress test electrocardiograms that display wide or unstable base lines, severe motion artifact or possible hidden S-T depression, please contact us. We think we can help.

Examples shown were produced under clinical conditions during an actual stress test procedure using the American Stress Test Electrode system.

We invite you to try the only electrode/cable system designed to match the "no compromise" nature of exercise stress testing. The fully shielded patient cable is adaptable to your present monitoring equipment, regardless of its make.

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- A total inservice for your staff.
- Information about our nationwide technical support program.

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The Stress Test Electrode is protected by NDM Corporation by the following U.S. Patents: 3,696,807; 3,701,346; 3,713,435.

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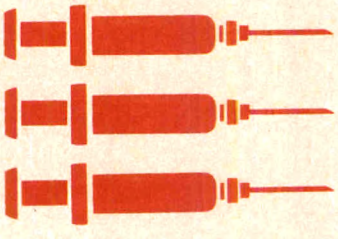
Effectiveness...

I.V. Administration Guidelines for Premature Ventricular Contractions and Tachycardia

1. Preparation of drug: Dilute before I.V. use.
2. Usual dosage range: 200-1000 mg.
3. Infusion rate: Not to exceed 25-50 mg. per minute. Total I.V. dose not to exceed 1000 mg.
4. Precautionary measures:
   a. Keep patient in supine position.
   b. Monitor electrocardiographically and discontinue if myocardial toxicity is evidenced.
   c. Measure blood pressure almost continuously and temporarily discontinue infusion if blood pressure falls more than 15 mm. Hg.

When therapeutic blood levels are required quickly, I.V. Injections

100 mg. every 5 minutes until arrhythmia suppressed (up to a maximum dose of 1 gram).



For ventricular arrhythmias

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by a variety of routes

I.V. Infusion

2-6 mg. per minute[1].
(42.8 μg./min./kg.)[2]

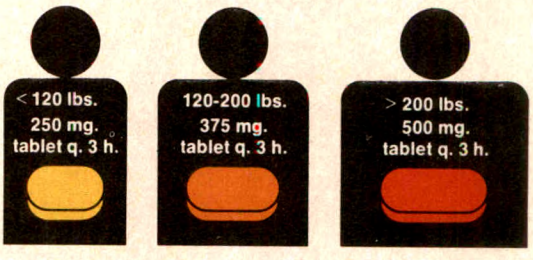
1. Wyman MG, Hammersmith L: Am J Cardiol 33:661-667, 1974
2. Bigger JT, Jr., Giardina EV: MCV Quart 9 (1): 65-76, 1973

Terminate I.V. infusion *4 hours before* oral regimen begun.

Oral Administration Guidelines to Provide 50 mg./kg./day* for Ventricular Arrhythmias

Ventricular Tachycardia
(give priming dose of 1 g. if patient has not received prior infusion)

Premature Ventricular Contractions



*This dosage schedule is for use as a guide for treating the average patient, but all patients must be considered on an individual basis.

Pronestyl®
(Procainamide Hydrochloride)
through the entire therapeutic course

See next page for brief summary.

PRONESTYL® TABLETS
(Procainamide Hydrochloride Tablets)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100.

PRONESTYL® INJECTION
(Procainamide Hydrochloride Injection U.S.P.)

Description: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml. ©1974 E. R. SQUIBB & SONS, INC. 444-009

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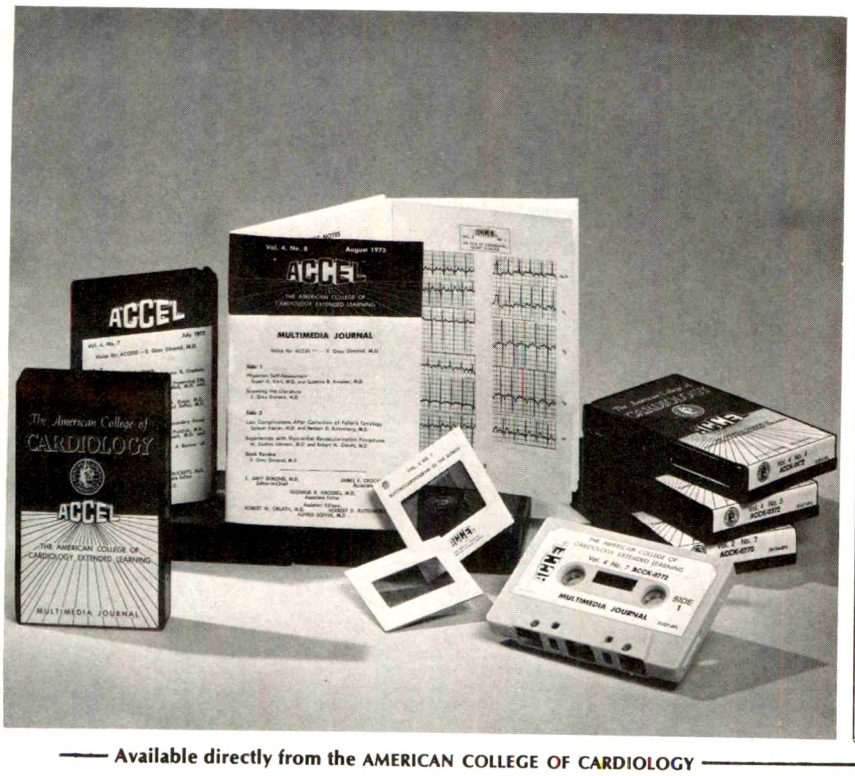

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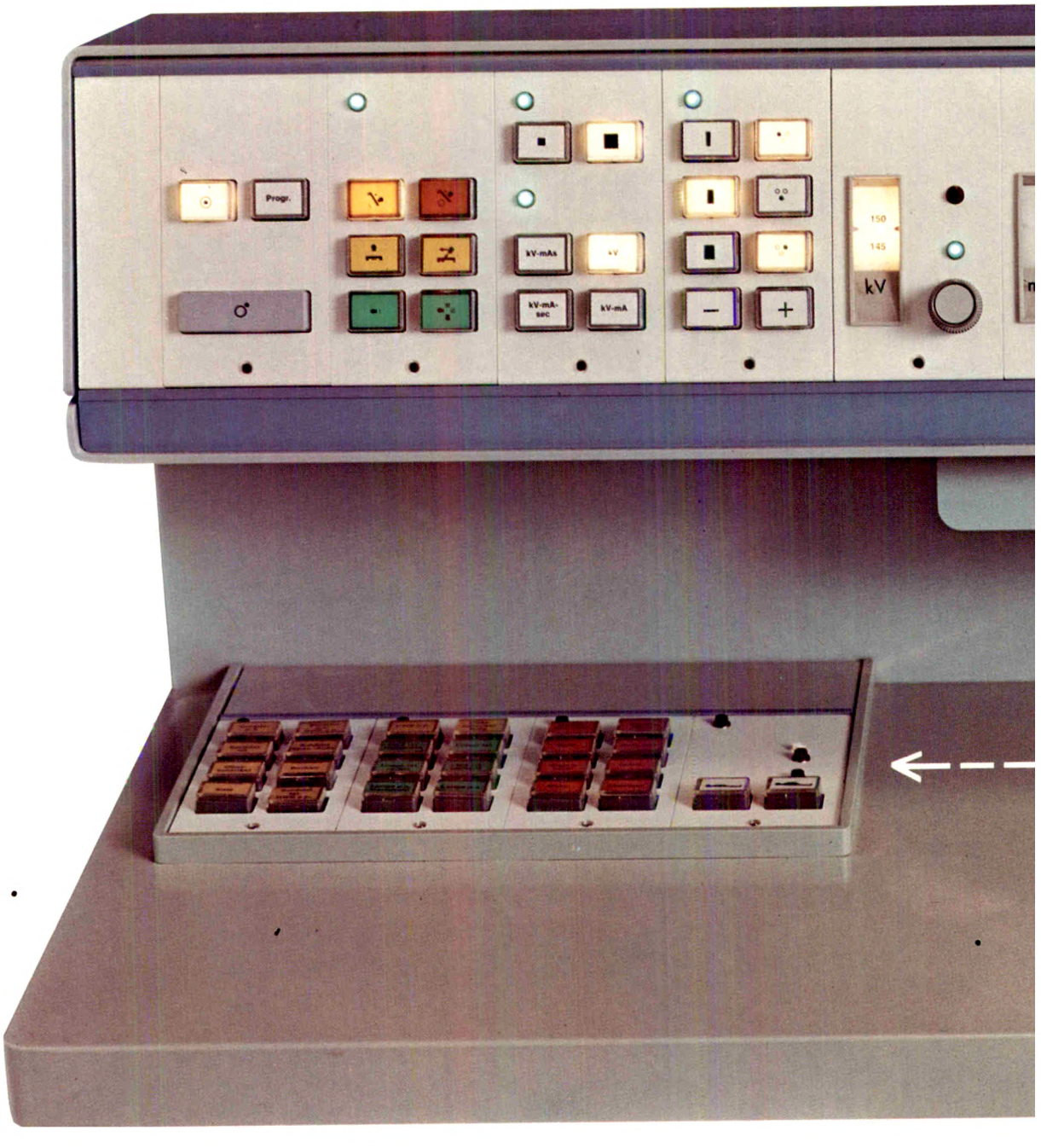

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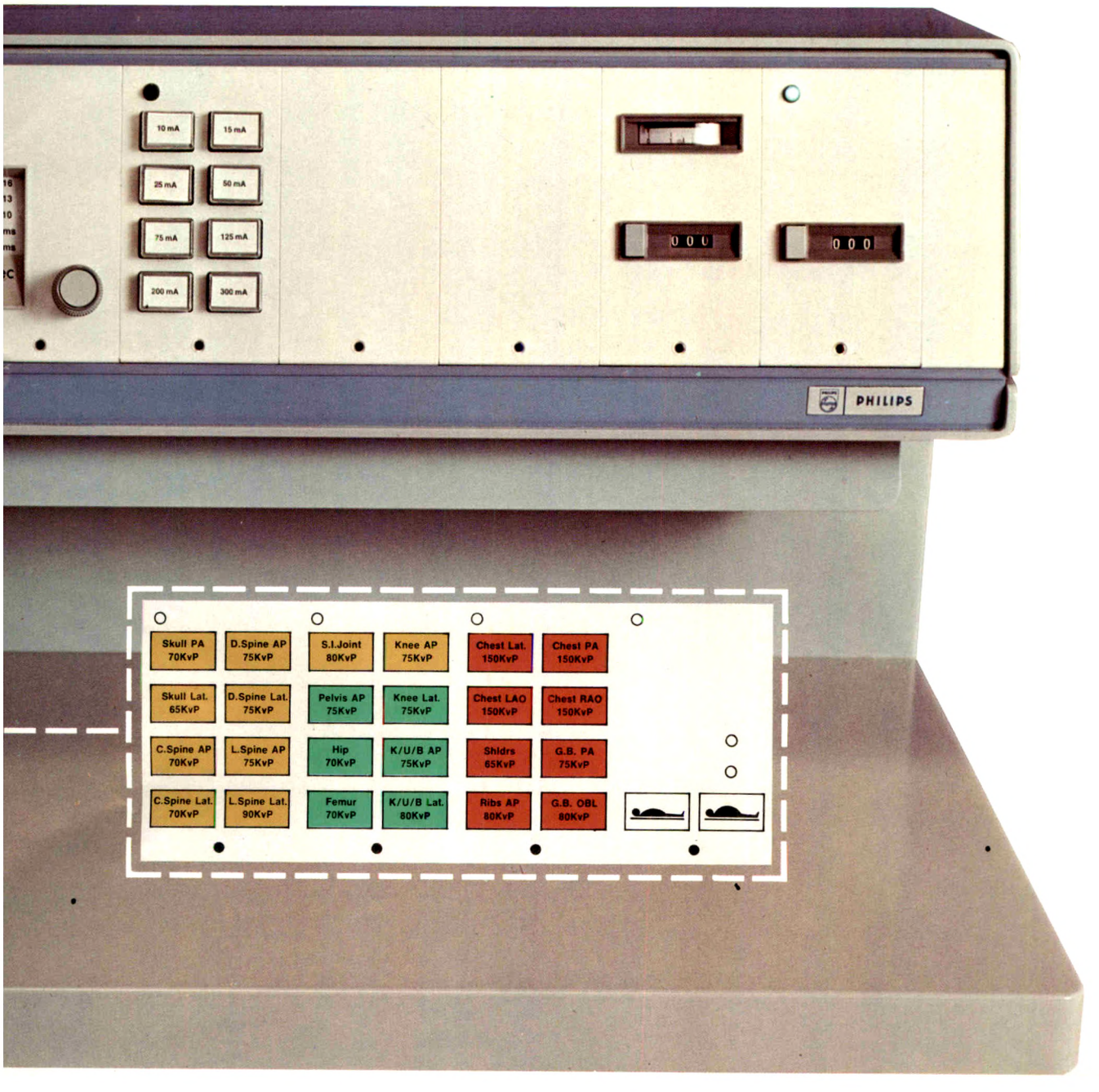


Congenital Malformations of the Heart

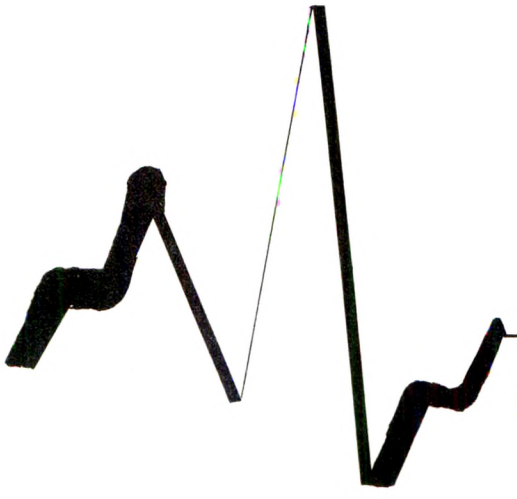
EMBRYOLOGIC, ANATOMIC AND OPERATIVE CONSIDERATIONS

Daniel A. Goor, M.D. and C. Walton Lillehei, M.D.

The first book to present a complete and comprehensive picture of the anatomy of complex cardiac malformations from their operative viewpoint. This information is based on the authors' first-hand experience in the fields of the embryology and pathology of the human heart and the operative repair of these malformations.

Major contributions were made by the authors in the understanding of the embryology of the conotruncus and the ventricles as well as in description of the developmental anatomy and classification of complex lesions as VSD, AV Canal malformation, Tetralogy of Fallot and Transposition complexes. The field of intracardiac repairs in congenital heart disease was pioneered by Dr. Lillehei.

May, 1975, 450 pages, illus. abt. $30.00/£14.40



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Edmund H. Sonnenblick, M.D., Editor
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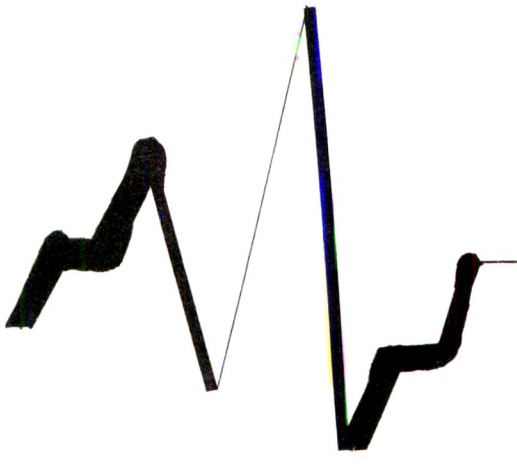

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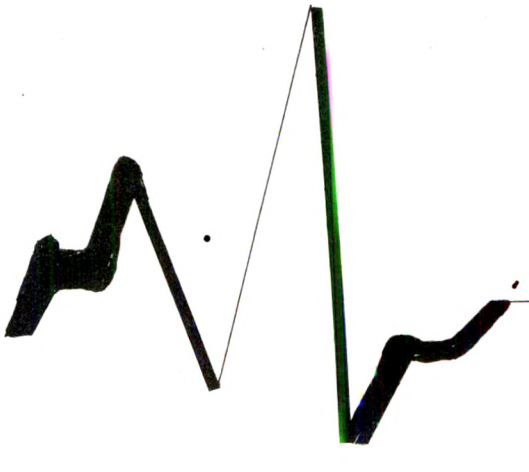

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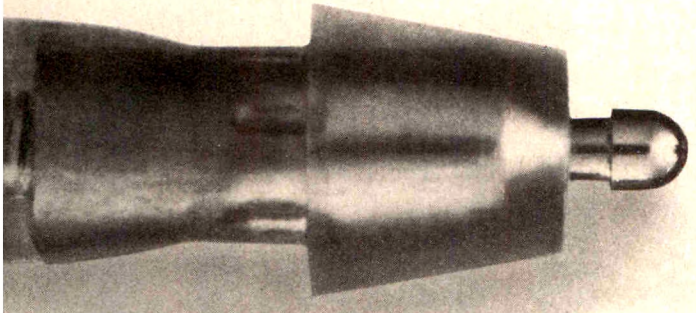

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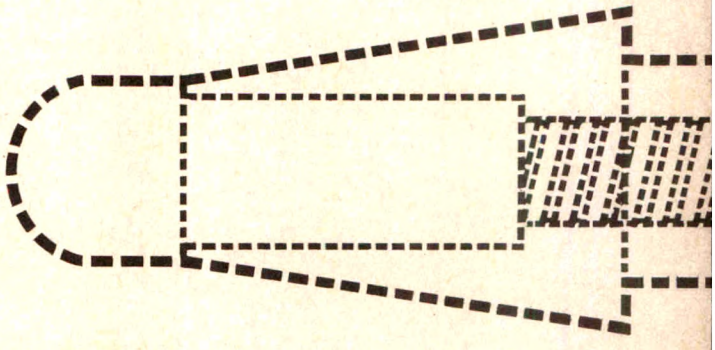

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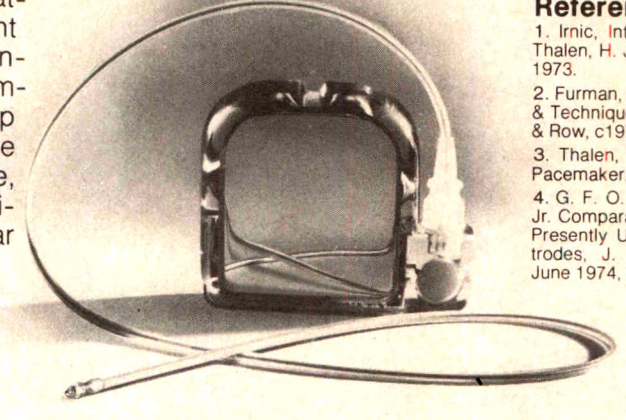

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Twenty-Fourth Annual Scientific Session American College of Cardiology Houston, Texas, February 10-13, 1975

SELECTION OF ABSTRACTS*

The abstracts selected for the 24th Annual Scientific Session of the American College of Cardiology are published in this issue of the American Journal of Cardiology. These 250 abstracts are impressive for their diversity of content and their scientific merit. New information generated in the research laboratory is vital for the growth of cardiology. For this reason, the Abstract Sessions form an essential component of the overall Scientific Program.

This year the Scientific Program Committee gave the investigator the option of selecting the grading category in which his abstract would be considered. Six grading categories were selected. These were Clinical Cardiology, Electrocardiography and Electrophysiology, Noninvasive Techniques, Basic Science, Pediatric Cardiology and Cardiovascular Surgery. A chairman was appointed for each of these grading categories. He and a team of experts then graded each abstract in their category. The grades were returned to the Bethesda office of the College where they were averaged. The abstracts were graded on a scale of 1 to 10, with 10 being the highest score attainable. All abstracts with a grade of 7.0 or above were accepted for presentation. The Scientific Program Committee then met at O'Hare Airport on October 19 and 20, 1974 to assemble the Abstract Sessions. Abstracts were grouped according to a basic theme or mutuality of interest and placed appropriately in the program. This year 29 percent of all abstracts submitted were found to be of sufficient merit to warrant presentation at the meeting. These 250 abstracts represent the largest number of abstracts ever presented at the College meeting.

Robert J. Luchi, MD, FACC
Scientific Program Chairman

COMPARISON OF HYPERTONIC MANNITOL AND POLARIZING SOLUTION ON LEFT VENTRICULAR FUNCTION DURING FOUR HOURS OF ISCHEMIA

S. Sultan Ahmed, MD; Bunyad Haider, MD, FACC; Benjamin Gamboa, MD; Timothy J. Regan, MD, FACC, New Jersey Medical School, Newark, New Jersey.

Enhanced glucose delivery to ischemic myocardium has been suggested to limit necrosis. To assess the influence on ventricular function, ischemia was produced by inflating a catheter tip balloon in the left anterior descending artery of intact anesthetized dogs and was maintained 4 hours. In 8 ischemic controls receiving isovolumic saline (Group 1) there was a progressive decline in stroke volume (SV) (indicator dilution) to 38±6%, ejection fraction (EF) to 37±11%, stroke work (SW) to 50±4%, mean rate of fiber shortening (MRFS) to 51±8%, associated with an EDP rise from 6±1 to 26±4 mm.Hg. Six animals received one liter of 10% glucose, 40 mEq/L potassium and 20 U insulin (GKI) after 20 min. of ischemia (Group 2). After 4 hours, SV, EF, SW and MRFS were restored to preischemic levels at an EDP of 11±1 mm.Hg (each P vs Group 1, <0.05). In 5 ischemic animals receiving an isovolumic solution of 20% mannitol (Group 3) to raise the serum osmolality to the same level as in Group 2. SV, EF, SW and MRFS declined similarly as in Group 1, despite a significantly lower EDP. Precordial EKG mapping revealed reduction in mean ST elevation following both GKI and mannitol, but with similar R wave loss as in Group 1. The greater hemodynamic efficacy of GKI compared to equiosmolar mannitol, would thus appear to be related to enhanced substrate delivery to the ischemic myocardium.

A COMPARATIVE STUDY OF ANTEGRADE AND RETROGRADE CONDUCTION PATTERNS IN MAN

Masood Akhtar, MD; Anthony N. Damato, MD; William P. Batsford, MD; Jeremy N. Ruskin, MD; J. Bimbola Ogunkelu, MD, Cardiopulmonary Lab, USPHS Hospital, Staten Island, NY

Patterns of antegrade (Ant) and retrograde (Ret)conduction (50 pts) and refractory periods (RP) (36 pts) were studied and compared using His bundle electrograms, incremental atrial and ventricular pacing and extrastimulus technique at comparable paced cycle lengths. During incremental pacing 36/50 pts demonstrated slower Ret conduction (group I) as evidenced by (A) earlier onset of Ret AV nodal Wenckebach phenomenon (WP) compared to Ant WP (25 pts) or (B) no ventriculo-atrial (VA) conduction, at all ventricular paced rates (11 pts); the site of Ret block being the AV node. In group II (8pts) Ant and Ret conduction was the same up to maximum paced rates of 160 beats/min. Six pts displayed better VA conduction than atrioventricular (AV) conduction (group III) by virtue of earlier onset of Ant WP compared to the Ret WP. During Ant RP the area of maximum refractoriness was the AV node in 16/36, the His-Purkinje system (HPS)in 6/36 and the atrial muscle in 14/36. During Ret RP, the AV node was the area of maximum refractoriness in 12/36, HPS in 12/36 and ventricular muscle in 10/36. In 2 pts initial site of Ret block could not be determined (i.e., AV node or HPS). The area of maximum refractoriness during both Ant and Ret RP was the same in 11 pts (AV node in 7 and HPS in 4), was different in 13 (AV node or HPS) and was either the atrial or ventricular muscle in 10. For the entire group the functional RP of the VA conduction system (CS) exceeded that of the AVCS. The available data suggest that (1) Ant conduction is better than Ret conduction in most pts, (2) prediction of refractoriness based upon conduction (both Ant and Ret) and prediction of Ret conduction and refractoriness from behavior of Ant conduction and refractoriness is difficult in individual pts.

* Abstracts are arranged alphabetically by first author.

EVALUATION OF RISK FACTORS AND FOLLOW-UP IN WOMEN FOLLOWING CORONARY ARTERY BYPASS

M. Al-Bassam MD, J. T. Dawson MD, E. Garcia MD, FACC, R. J. Hall MD, FACC, G. L. Hallman MD, FACC, D. A. Cooley MD, FACC; Texas Heart Institute, Houston, Texas

In a previous report from this institution, increased early mortality (within 30 days postop) after coronary artery bypass (CAB) in females (F) was noted. Of 2714 patients (pts) who underwent CAB through Dec 1973, 354 (13.1%) were F. Of the 354 pts, 35 F (9.9%) in contrast to 134 males (M) (5.7%) died in the early postop period. Characteristics of the first 1,372 pts were evaluated to elucidate increased risk factors.

Factor	Males	(%)	Females	(%)
Diabetes mellitus	110	(9.0)	32	(21.2)
Hypertension	71	(5.8)	37	(31.1)
Preinfarction angina	78	(6.4)	29	(11.6)
Recent infarction	90	(7.4)	20	(13.2)
ECG: ST injury	320	(26.2)	66	(43.7)
T ischemia	318	(26.0)	62	(41.0)
Avg. coronary artery score	9.24		7.95	
Autopsy cardiac weight	545 gm		453 gm	

Other characteristics evaluated but noted not to be significantly different in the 2 groups included lipid abnormalities, preoperative congestive failure, history and/or ECG findings of old infarction, A-V and I-V conduction defects, preoperative arrhythmias, LVEDP and ischemic pump time. Late attrition (after 30 days) over a 4-year period was not notably different in the 2 groups. Although less common, symptomatic coronary artery disease is more frequently a part of systemic vascular disease and presents in a more aggressive form in F leading to an increased early mortality after CAB. Technical difficulty due to smaller coronary vessels in F may also contribute to the operative risk. The increased early mortality of CAB in F must be considered when surgery in contemplated.

CLINICAL SIGNIFICANCE OF STRESS INDUCED MOBITZ-I A-V BLOCK (AVB) IN PATIENTS WITH DISABLING ANGINA PECTORIS

Federico G. Alfaro, MD, Virendra S. Mathur, MD, Albert E. Raizner, MD, Robert A. Chahine, MD, Alfredo C. Montero, MD, Robert J. Luchi, MD, FACC, V.A. Hospital and Baylor College of Medicine, Houston, Texas

To evaluate the significance of AVB induced by stress of atrial pacing (P), 200 consecutive patients (PTS) with chest pain undergoing coronary angiography and P were studied. Eighteen PTS developed AVB before achieving a heart rate (HR) of 140/minute, the mean HR at which AVB appeared was 113 (range 85-140). Eight PTS who at 1 year were re-studied by P had a variable response. The mean age was 53 years (range 39-62). All 18 PTS had disabling angina pectoris. Fifteen (83%) had old inferior infarction by ECG and 1 developed 3 weeks later. Coronary angiography disclosed critical stenosis or complete occlusion of right coronary artery (RCA) in 17 PTS (94%). The anterior descending and circumflex coronaries were less frequently involved (61% and 39%). All PTS were followed (mean 16, range 5-31 months). None of the PTS, including 10 who were receiving digoxin, revealed either increase of P-R interval or AVB. One had transient P-R prolongation during acute inferior infarction, 2 with abnormal P-R interval did not progress. Multi-stage treadmill test was performed in 17 PTS, 14 PTS (83%) achieved HR higher than peak HR during P and in these the P-R interval shortened in 12 and was unchanged in 2.
Conclusion: AVB induced by P at a HR of 140 or less, in PTS with angina pectoris was associated with RCA disease and inferior infarction. A-V conduction did not deteriorate in any patient and exercise tachycardia (mean 137, range 92-170) did not produce AVB. The phenomenon per se should not demand limitation of exercise and does not indicate that symptomatic or advanced block is imminent.

CORONARY ANATOMY AND ARTERIOGRAPHY IN PATIENTS WITH UNSTABLE ANGINA PECTORIS.

Harold W. Alison, MD; Roger E. Moraski, MD; John A. Mantle, MD; Charles E. Rackley, MD, FACC; Richard O. Russell, Jr., MD, FACC. University of Alabama Medical Center, Birmingham, Alabama.

One hundred eighty-two patients (pts) with the clinical syndrome of unstable angina pectoris (UAP) were evaluated to determine the spectrum of coronary artery disease (CAD) and the incidence of in-hospital myocardial infarction (MI) and death. UAP was considered as either angina of recent onset, worsening of effort angina, and/or onset of rest angina. Following an observation period during which there were no evolutionary ST-T wave changes and no rise of SGOT, Judkins' coronary arteriograms and left ventricular (LV) angiography were performed. Both cineangiograms (60 frames/sec) and large film angiograms (2-6 frames/sec) were available for precise definition of coronary anatomy. Lesions of the major coronary arteries were graded as severe (70-100% stenosis of the arterial lumen) and mild (25-70% stenosis). Group A consisted of 153 pts with severe CAD; 20 pts (13%) also had significant disease in the left main coronary artery (LMCA). One hundred thirty-six pts had coronary anatomy suitable for saphenous vein bypass grafting (SVG) and 17 pts were considered unsuitable (14 pts had diffuse distal vessel disease and 3 pts severe LV dysfunction). Group B consisted of 29 pts; 11 pts had mild CAD and 18 pts normal coronary arteriograms. Following arteriography, 5 pts in Group A sustained an acute MI and survived; 6 pts died (5 had significant disease in the LMCA). No pts in Group B sustained an MI or died. Thus, 84% of pts that presented with UAP had severe CAD and 75% had coronary anatomy suitable for SVG. Eleven percent of pts had disease in the LMCA and 10% normal coronary arteriograms. These data also indicate that the incidence of MI following angiography in UAP is low and that deaths are usually associated with LMCA stenosis.

LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH ANGINA-LIKE CHEST PAIN AND ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES

Pablo I. Altieri, MD; Mary Ellen M. Pollack; Richard F. Leighton, MD, FACC, The Ohio State University Hospital College of Medicine, Columbus, Ohio.

The high incidence of electrocardiographic and metabolic abnormalities in patients (pts) with angina-like chest pain (ALCP) and angiographically normal coronary arteries (ANCA) led us to look for evidence of left ventricular (LV) dysfunction in 34 such pts. A quantitative analysis of segmental wall motion (SWM) was performed from tracings of single plane LV cineangiograms (C). Normal values for SWM were established in 20 of the 34 pts (normal group, NG) who had ejection fractions (EF) > 0.60, av 0.68 ± 0.05. Hypokinetic segments (HS) were defined as those where the amplitude of systolic motion was less than 2 standard deviations from the NG mean. When this method was applied to the LVC of the other 14 pts who had EF's < 0.60, av 0.55 ± 0.03, $p < 0.001$, 11 pts were found who had HS. The 7 males with HS also had greater end-diastolic (ED) volumes than the NG, av 102 ± 30 vs 67 ± 12 ml/sqM, $p < 0.001$, while the 4 females with HS did not. Pts with HS could not be separated from the NG by history, physical examination, chest x-ray, electrocardiogram, treadmill exercise test, systolic time intervals, coronary sinus lactate studies or by LV ED pressure before or after LVC. Thus careful analysis of LVC in pts with ALCP, ANCA and EF's < 0.60 has revealed further evidence of LV dysfunction. While the significance of these findings remains unclear, such pts should probably not be considered normal but should have further medical follow-up.

QUANTITATIVE ASSESSMENT OF LEFT VENTRICULAR INTEGRITY AFTER MYOCARDIAL INFARCTION ASSOCIATED WITH AORTOCORONARY BYPASS GRAFT SURGERY.

Ezra A. Amsterdam, MD, FACC; Anthony N. DeMaria, MD; William Markson, BA; Richard R. Miller, MD; Dean T. Mason, MD, FACC. U.C. Davis, Calif.

Although intraoperative myocardial infarction (MI) has been noted with varying frequency during coronary artery bypass graft surgery (CBGS), objective and quantitative analysis of related left ventricular (LV) damage is lacking. Therefore, in 16 patients (pts) in whom MI occurred during CBGS, as indicated by development of pathologic Q wave, pre and postoperative (mean 6 mos) LV function was evaluated. In 10 pts the graft (G) was patent to the area of MI (7 anterior, 3 inferior LV). In this group, preoperative abnormal contractile pattern (CP) of infarcted LV segment (seg) improved in 7 pts and was unchanged in 3 pts: group mean systolic motion (SM) (as percent shortening) of the involved LV seg increased from 30% preoperatively to 38% postoperatively ($p<.01$); LV ejection fraction increased from .50 to .55 ($p<.05$); LV end diastolic pressure (EDP) (10 mm Hg) and stroke index (SI) (44 ml) were unchanged ($p>.05$). In a second group of 6 pts, intraoperative MI (5 anterior, 1 inferior) was remote from the LV seg supplied by a patent G ($n = 3$) or in the area of an occluded G ($n = 3$). In this group, CP of infarcted LV seg deteriorated in all pts: SM of involved LV seg fell from 32% preoperatively to 22% postoperatively ($p<.05$); LV ejection fraction decreased from .52 to .40 ($p<.05$); LVEDP (12 mm Hg) and SI (42 ml) were unchanged. Intraoperative MI did not deleteriously affect LV function when the region of infarction was supplied by patent G. However, when MI involved an area of LV remote from a patent G or in the area associated with an occluded G, significant deterioration in LV contractile performance resulted.

LATE RESULTS OF SURGICAL REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES (TGA).

Robert Antar, M.D., Ehud Krongrad, M.D., Frederick O. Bowman, Jr.,M.D., James R. Malm, M.D. Welton M. Gersony, M.D., College of Physicians and Surgeons, Columbia University, New York, N.Y., 10032

Forty-one patients were followed 6 months to 3 1/2 years (mean= 20 months) after surgical repair of TGA by means of the Mustard operation. Thirty-two had intact ventricular septum. Three pts. died during this period, one each as the result of systemic venous obstruction (SVenO), pulmonary venous obstruction (PVenO), tricuspid insufficiency (TI). Eight of the 38 survivors displayed junctional bradycardia (JB) during the followup period. Five developed this dysrhythmia in the immediate postoperative period, but in three instances JB was initially documented more than one year after surgery. One patient had early first degree A-V block and another right bundle branch block (RBBB). Two patients developed RBBB as a late postoperative manifestation.

Twenty-one patients underwent postoperative cardiac catheterization. Eleven of the 21 pts. had residual hemodynamic abnormalities; 4 of these had SVenO, 5 had PVenO, (3 severe), 1 had TI, and one had mild pulmonary stenosis. Residual shunts were documented in 4 of these pts. Seven of the 11 required re-operation. The other 10 pts. had no significant cardiac abnormalities. This data indicates that postoperative complications following the Mustard operation for repair of TGA are not infrequent. SVenO and PVenO were the most common residual anatomic abnormalities and JB was the rhythm disturbance most likely to be encountered. This arrhythmia might not be apparent until late in the postoperative course.

CLINICAL USE OF FROZEN VIABLE HUMAN HEART VALVES

William W. Angell, MD, Christopher O. Hawtrey, PhD, and Robert D. Wuerflein, MD, Veterans Administration Hospital, Palo Alto, Calif., and the Santa Clara Valley Medical Center, San Jose, Calif.

Correction of heart disease using viable human aortic valves has produced favorable results, but the difficulty in storing fresh valves for long periods of time has necessitated the development of cryogenic methods of preservation. Human valves obtained using sterile technique are processed and stored to supply free and mounted grafts. They are placed in antibiotic solution with DMSO as cryoprotectant and then in vapor phase liquid nitrogen. When thawed the valves retain important morphological and histological characteristics and qualities of freshly obtained valves. Tissue culture confirms viability. Heart valves have been stored with proven viability for seven months, but the limit of storage has yet to be determined. Thirty patients have received frozen human valves in the eighteen months they have been available. Twenty-seven survived with one reoperation due to perivalvular leak. Insignificant murmurs developed in some patients. There were no valve failures in the three patients who died. Storage of human tissues at liquid nitrogen temperatures confers two important advantages to the recipient: 1) Viability is maintained, which is vital to the longevity of the transplant, and 2) Adequate choice by the surgeon of valve size and blood type, both of which are important factors in surgical success.

TEN TO 40 YEAR FOLLOW-UP OF 69 PATIENTS WITH SYSTOLIC CLICK WITH OR WITHOUT APICAL LATE SYSTOLIC MURMUR*

Nancy Haley Appelblatt, B.S.* Park W. Willis, III, M.D. Jack A. Lenhart, B.S.* Jeffrey I. Shulman, M.D.* Joseph A. Walton, Jr., M.D., Univ. of Michigan, Ann Arbor, Mich.

The prognosis for individuals with systolic click (SC) with or without apical late systolic murmur (SM) is not known. Records of 161 patients with SC with or without SM were drawn from University Hospital files (1930-1964). Follow-up information was obtained on 35 men and 34 women. Death certificates (and medical records) were obtained on 9 men and 6 women. Medical information was obtained on the 18 living patients who could not be examined. Thirty-six patients had history, physical exam and ECG. Using life expectancy tables, 14 of these 69 patients were expected to be dead at time of follow-up; 15 actually were dead. The average age at death was 68 years. A 46 year old woman died of a ventricular arrhythmia. Of 36 examined patients, 16 had SC only on first exam and 20 had SC and SM or SM only (1 pat.). Among the group with SC only (mean follow-up - 25 yrs), 12 developed multiple clicks or SM and four (all men) developed pansystolic murmur. Of those with SM (mean follow-up - 23 yrs), 7 had no change, 6 developed multiple SC or louder murmur and 7 (6 men, 1 woman) had much louder or longer SM. Only one patient with marked increase of murmur had CHF symptoms. Two patients had SBE prior to first exam, none had SBE or ruptured chordae tendineae (RCT) during follow-up. Classical angina pectoris was present in 3/36 patients and there was subjective and objective evidence of arrhythmia in 8/36. Thus, among patients with SC/SM we found 1) men more often had progression of auscultatory findings than women, 2) survival was not less than expected, 3) sudden cardiac death was rare, 4) neither RCT nor SBE was encountered. *Supported by Michigan Heart Association Research Grant and Medical Student Research Fellowships

IMPORTANCE OF SMALL INCREMENTS OF OXYGEN DELIVERY IN PROTECTING ISCHEMIC MYOCARDIUM. Carl S. Apstein, M.D.;Marc Mueller, BA; Lawrence Deckelbaum, William B. Hood, Jr., M.D., Boston University, Boston, Massachusetts.

In order to separate the lack of O_2 delivery from other consequences of ischemia(decreased substrate delivery and metabolite washout),the mechanical effects of hypoxemia and ischemia were compared in isolated,isovolumic(balloon in LV)rat hearts perfused with Krebs-Ringer buffer. Control developed pressure(DP) was 73±2mmHg(n=6) with coronary flow (CF)=12ml/min,(pO_2=600mmHg,O_2 delivery=227 µl/min). Thirty minutes of hypoxemia(n=6) (pO_2<10mmHg,CF=12 ml/min,O_2 delivery=2µl/min) or severe ischemia(n=14)(CF=0-.04ml/min, pO_2=600mmHg, O_2 delivery=0-1µl/min) caused a marked depression of DP to<5mmHg, with recovery to 35% of control DP in both groups. Both hypoxemia and ischemia caused contracture("stone heart" behavior) so that isovolumic diastolic pressure increased from a control of 0±3 mmHg to 61±10 (p<.01) with hypoxemia, and 32±4 (p<.01)with ischemia. With reoxygenation, contracture was promptly reversed after hypoxemia but reperfusion after ischemia increased contracture to 64±6mmHg(p<.01). Pacing threshold increased from a control of 1.5V. to 20±4V. with hypoxemia (p<.01) and >25V. with ischemia (p<.01).

Thus both hypoxemia and ischemia caused marked depression of contractile function, contracture, and increase in pacing threshold. An increase in ischemic CF to 3% of control(n=6)(CF=0.4ml/min, pO_2=600mmHg, O_2 delivery=7µl/min)did not improve DP during ischemia, but permitted complete recovery of DP with reflow, caused contracture of 49±7mmHg, but eliminated the intensification of contracture with reperfusion, and prevented any increase in pacing threshold during ischemia. These results indicate that oxygen-poor coronary flow is of little benefit to the myocardium with sustained hypoxia, but that very small increases in ischemic O_2 delivery have a profound effect on subsequent recoverability.

EFFECTS OF THE PACING SITE ON A-V CONDUCTION AND REFRACTORINESS IN PATIENTS WITH SHORT P-R INTERVALS AND NARROW QRS COMPLEXES
Juan Aranda, MD; Federico Moleiro, MD; Agustin Castellanos, MD, FACC and Benjamin Befeler, MD, Veterans Administration Hospital and the Univ. of Miami, Miami, Florida.

His bundle electrograms were recorded in four patients with short P-R(120 msec or less),short A-H (less than 55 msec), normal H-V and narrow QRS complexes. Atrial stimulation was performed from the high right atrium(HRA), coronary sinus (CS) and, when necessary, from low right atrium (LRA). During sinus rhythm A-H was at least 10 msec shorter from CS. In three patients A-H Wenckebach developed at rates greater than 200 per minute. Increments in A-H were greater from HRA(10 to 100 msec)than from CS(15 to 60 msec). Pacing with the extrastimulus method showed that the minimal H1-H2 interval (functional refractory period) of the A-H tissues were 15 to 40 msec shorter from CS. The corresponding effective refractory period (ERP) could not be measured because of differences in atrial ERP between paced sites. One case had exclusive accessory pathway from CS, exclusive A-V nodal conduction from HRA and combined conduction from LRA.In a fourth patient A-H conduction was possible through both pathways from HRA and CS but activation of A-V node could not occur from LRA. It is concluded that the site of atrial stimulation influences A-H conduction possibly by changing the site and(or) mode of entry into the pathway(s) responsible for the short P-R syndrome.

PROSTHETIC VALVE ENDOCARDITIS: A STUDY OF 18 PATIENTS AT NECROPSY
Ernest N. Arnett, MD; William C. Roberts, MD, FACC, National Heart and Lung Institute, Bethesda, Md.

Although introduced 15 years ago, prosthetic valve endocarditis (PVE) has received little detailed morphologic study. Of 18 necropsy patients (pts) with PVE, 1 valve was replaced in 14, and 2 valves in 4. Rigid framed prostheses (Starr-Edwards=12; non-tilting disc=2; tilting disc=4) were used. The aortic (A) prosthesis was infected in 11 pts; the mitral (M) in 7. Of 3 pts with both M and A prosthesis, only the A was infected; of 1 pt with both tricuspid and M prostheses, only the M was infected. The interval between operation and death was <3 mo. in 9 pts and between 4 and 120 mo. in 9 pts. The source of the infection was apparent in 13 and unknown in 5 late deaths. The infecting organisms were: *staphylococcus epidermidis* (8 pts), *S. aureus* (5), *proteus mirabilis* (1), *Klebsiella sp* (1), *serratia marcescens* (1), diphtheroids (1), *aspergillus sp* (1). In each, the infection was located at the site of attachment of the prosthesis causing detachment with resulting paravalvular aortic regurgitation in all but 1 of the 11 pts with A prostheses. Evidence of paravalvular leak occurred in only 1 of the 7 pts with M PVE but anular prosthetic sutures were loosened in all. The 7 with M PVE died primarily from prosthetic obstruction due to large vegetations, and none had conduction disturbances. Ten of the 11 with A PVE died from prosthetic regurgitation and 8 had conduction disturbances from spread of the infective process to adjacent conduction tissue. Once the infection becomes established beneath the site of attachment of the prosthesis, antibiotics appear incapable of eradicating the infection. The rigidity of the prosthetic anulus appears responsible for causing extensive local spread of the infective process.

MASS SCREENING FOR CORONARY RISK FACTORS
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The incidence of coronary risk factors was evaluated in 2,524 asymptomatic adults in Long Beach, Calif. The results were given to the participants and their physicians. Half the subjects were mailed literature and invited to attend lectures about reduction of risk factors. One year later, 1,817 adults were rescreened. The fasting serum cholesterol level was above 250 mg% in 522 adults (28.7%) during screen 1 and in 556 adults (30.5%) during screen 2 (P not significant). The fasting serum triglyceride level was ≥ 150 mg% in 362 adults (19.9%) during screen 1 and in 475 adults (26.1%) during screen 2 (P < 0.001). A blood pressure above 140/90 mm Hg was observed in 156 adults (8.6%) during screen 1 and in 257 adults (14.1%) during screen 2 (P < 0.001). There were 851 cigarette, cigar, or pipe smokers (46.8%) during screen 1 and 762 smokers (41.9%) during screen 2 (P < 0.01). The fasting blood sugar was above 120 mg% in 30 adults (1.7%) during screen 1 and in 42 adults (2.3%) during screen 2 (P not significant). The weight was ≥ 20% above desirable weight in 270 adults (14.9%) during screen 1 and in 274 adults (15.1%) during screen 2 (P not significant). No risk factors were found in 600 adults (33%) during screen 1 and in 554 adults (30.5%) during screen 2 (P not significant). The number of adults with 1, 2, 4, 5, and 6 risk factors during screens 1 and 2 was not significantly different. The number of adults with 3 risk factors was 165 (9.1%) during screen 1 and 204 (11.2%) during screen 2 (P < 0.05). The Long Beach Heart Association mass screening program for coronary risk factors was ineffective in reducing the number of risk factors.

AORTA-TO-CORONARY ARTERY SAPHENOUS VEIN BYPASS GRAFTS: COMPLETE VERSUS INCOMPLETE REVASCULARIZATION

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A series of 159 patients (pts) with postop. graft angiograms (PGA) 1-42 mo (median 11 mo) after coronary surgery were studied. To evaluate the completeness of myocardial revascularization, a vessel was considered left ungrafted (VLU) if (1) it had an obstruction >50% and was ungrafted or (2) the graft to the artery was occluded on the PGA. Four groups evolved: Gp I (44 pts), 0 VLU; Gp II (68 pts), 1 VLU; Gp III (35 pts), 2 VLU; and Gp IV (12 pts), 3 VLU. The clinical results in each group were correlated with the number of vessels diseased (VD). When revascularization was complete, of the 44 pts in Gp I, 36 pts (12, 1-VD; 14, 2-VD; 10, 3-VD) were pain-free (82%). In Gp II, the 22 with 3-VD showed significant improvement, as 18 (77%) were pain-free (such pts had 2 normally functioning grafts); the 36 with 2-VD were equally divided in the pain-free, improved, and unimproved categories (all had 1 graft patent); of the 10 with 1-VD (only graft occluded), only 2 were pain-free. In Gp III, 7 (64%) of the 11 pts with 2-VD (all grafts occluded) were unimproved, while of the 24 pts with 3-VD, 12 had improved, and 4 (17%) were pain-free (these pts had only 1 patent graft). In Gp IV (12 pts with 3-VD), 6 were unimproved, and only 1 was pain-free. Thus, by the evaluation of postop. symptoms at PGA, a high correlation existed between complete relief of angina and a complete revascularization. Such an approach allows a more precise analysis of whether the pt at symptom evaluation has remaining areas of myocardium with angiographic evidence of ischemia.

MICROELECTRODE STUDY OF BLOCK MECHANISMS IN PURKINJE TISSUE SEGMENTS EXPOSED TO A SODIUM-FREE MILIEU

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We employed an electrical blocking current in earlier microelectrode studies of block mechanisms. More recently a three chamber perfusion bath was devised in which a single Purkinje bundle can be exposed to three individual superfusates. Using this tripartite chamber, the middle chamber is perfused with Na^+ free Tyrode solution (Na^+ replaced with THAM), producing inactivation of the Purkinje tissue segment contained therein. Segments proximal and distal to the middle chamber are perfused with normal Tyrode, and are fully active. Fibers are electrically stimulated (0.5 - 2 pulses/sec) in the proximal active segment and transmembrane recordings are taken from all three segments of the Purkinje bundle. In a total of ten preparations simple conduction delay, Wenckebach periodicity, 2:1 block, and higher grades of block (3:1 to complete) were observed. The results indicated that the degree of block obtained was inversely related to the slope of slow diastolic depolarization in the segment distal to the blocked region. Slow diastolic depolarization was a principal factor in sustaining periodic impulse conduction for two reasons: (1) it allowed a progressive rise of the resting membrane potential toward threshold at the distal block boundary; (2) there was augmentation of the transmitted electrotonic potential in accordance with voltage dependent changes in membrane resistance. This basically different method of producing block lends further support to the previously formulated hypothesis that conduction delay through a blocked segment of Purkinje tissue is electrotonic, and that slow diastolic depolarization is of key significance in the maintenance of impulse transmission.

FUNCTIONAL INSULATION OF THE RIGHT BUNDLE BRANCH

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Intracellular microelectrodes were used to assess electrotonic interaction between the intramyocardial segment of the canine right bundle branch (RBB) and the surrounding septal muscle (RVM) as a possible cause of RBB block aberrancy. A total of 15 in vitro experiments were performed. The RBB does not supply conducting fibers directly to the RVM in this segment, and by use of appropriate stimulus intensities, we stimulated the RBB without activating RVM and stimulated RVM without activating RBB. RBB and RVM were stimulated at similar constant rates, but independently. Stimulation of RVM was programmed to occur at numerous points before, during, and following the RBB action potential. There were no changes in RBB resting and action potential, $\dot{V}_{max}$ phase 0, RBB conduction time, or action potential duration of RBB measured at 95% repolarization, regardless of the temporal relationship between RVM and RBB activation. Moreover, using a single microelectrode for simultaneous intracellular stimulation and recording, there were no changes in RBB current threshold requirements for all-or-none depolarization (excitability). We conclude that, in this preparation, the proximal canine RBB is functionally insulated, and that the characteristics of conduction in the RBB are not influenced electrotonically by the electrical state of the RVM.

DETERMINANTS OF REVERSIBLE ASYNERGY: THE NATIVE CORONARY CIRCULATION

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To determine the effect of native coronary circulation on reversibility of asynergy, ventriculograms before and after sublingual nitroglycerin were performed in 51 patients with coronary artery disease. Severity of stenotic lesions and caliber of the distal coronary vessels were determined by comparison with external catheter tip diameter corrected for magnification. Of 42 asynergic zones (AZ) associated with $\geq$90% proximal coronary occlusion (occl), 27 (64%) were akinetic or dyskinetic while 11 of 38 (29%) with <90% occl showed akinesis ($p<.005$). Collaterals (collat) were observed in 23 of 42 (55%) AZ with $\geq$90% occl in contrast to only 11 of 38 (29%) AZ with <90% occl ($p<0.05$). Of AZ with both $\geq$90% occl and collat, 74% were reversible in contrast to 11% without collat ($p<.001$). In AZ without collat 64% with <90% occl were reversible in contrast to only 11% with $\geq$90% occl ($p<.001$). Pathologic Q waves were associated with 24 of 42 (57%) AZ with $\geq$90% occl compared to only 10 of 38 (26%) with <90% occl ($p<0.01$). Q's were associated with a significant decrease in reversibility of AZ regardless of the degree of coronary occl. Excluding AZ with both collat and Q's, 79% with <90% occl were reversible in contrast to only 37% with $\geq$90% occl ($p<.05$). Caliber of the distal vessel was similar in reversible (1.5 ± 0.3mm) and irreversible (1.4 ± 0.3mm) zones. In summary, $\geq$90% proximal stenoses are associated with severe asynergy which is less likely to be reversible compared to asynergy with <90% coronary occlusion. In the presence of $\geq$90% occlusion, coronary collaterals significantly improve the chances of reversibility and thus appear to serve a protective function; however, caliber of the distal vessel per se does not affect reversibility.

EFFECT OF TACHYCARDIA ON REGIONAL LEFT VENTRICULAR BLOOD FLOW AFTER CORONARY ARTERY OCCLUSION.

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Tachycardia increases muscle damage during acute myocardial infarction. Possible mechanisms include increased oxygen demands and/or impairment of collateral blood flow. To define this further, flows to ischemic (I) and non-ischemic (NI) regions of left ventricle (LV) were measured with 7-10 μ diameter radioactive microspheres 1 hour after coronary artery ligation at baseline rates (118±6 beats/min) and again during atrial pacing (rate +40%, 165±9 beats/min) in 9 open-chested dogs. Aortic and left atrial pressures and cardiac output were unchanged. In NI regions flow increased from 0.77 to 1.05cc/min/g (+36%, $p < 0.005$) with subepicardial (EPI) flow increasing more than subendocardial (ENDO) flow (39% vs 31%). In I regions overall flow did not change significantly (0.27 to 0.26cc/min/g) but a redistribution from ENDO to EPI was seen. ENDO flow fell 25% (0.16 to 0.12cc/min/g, $p < 0.02$) and EPI flow increased slightly; ENDO/EPI fell in 8/9 dogs (mean 0.54 to 0.43, $p < 0.01$). ΣST segment elevation in epicardial electrograms increased from 33.1 to 91.2 mV (+176%, $p < 0.001$) and the number of epicardial sites with significant elevation increased from 4.3 to 8.2 (+91%, $p < 0.001$).

The results indicate that total collateral flow does not fall significantly with moderate increases in heart rate. However, the ENDO/EPI maldistribution present in I regions is accentuated during tachycardia leading to further reduction in ENDO flow. This may account for part of the injurious effect of tachycardia in acute myocardial infarction and may help explain ENDO ischemia in angina pectoris. Possible mechanisms include reduced diastolic time and a "steal" of flow from ENDO to EPI.

A NEW METHOD FOR CALCULATING RIGHT VENTRICULAR VOLUME IN MAN FROM BIPLANE RADIOGRAPHS

BY J.G. Boak,MD; A.A. Bove, PhD,FACC; T. Kreulen, MD, FACC; J.F. Spann, MD, FACC, Temple University, Philadelphia, Pa.

Although indices of right ventricular (RV) function such as stroke work, ejection fraction, and wall stress require measurement of right ventricular volumes (RVV),no radiographic method exists for finding RVV in adult man based on RV internal geometry. RV geometry and RVV were studied using 7 silicone rubber casts from adult human RV's with volumes measured by water displacement (V_d) of 30 to 144 ml. Radiographs of the casts were made in the right and left anterior oblique (RAO and LAO) projections, the height (H) of the LAO image and the planimetered areas (A_{RAO}, A_{LAO}) measured, and the results corrected for xray magnification. The casts were cut into 8-10 sections perpendicular to a line from the apex to the junction of the inflow and outflow tracts. For each section the maximum distance (w) parallel to the septum, maximum depth (b) perpendicular to w, and planimetered area (A_S) were measured. It was found that $A_S = kwb$, where k was a constant for all sections. For an entire ventricle the volume, $V = \Sigma A_S h$ where h=section thickness, or by substitution $V = k\Sigma hwb$. This gave a calculated volume within 4% of V_d. Using this equation, a method was developed for measuring RVV from the biplane radiographs. From the xray $\Sigma hw = A_{RAO}$, and since b was found to be nearly constant for a particular ventricle, then $b = A_{LAO}/H$. By substitution $V = kA_{RAO}A_{LAO}/H$. When $k = \pi/4$, this equation permitted calculation of a cast's volume from its radiographs (V_x) to within 10 ml of its V_d with 95% certainty: over a range of 30 to 140ml, $V = 0.95V_d$ ($R = 0.994$, SEE=5.1 ml, $p < 0005$). This study of RV geometry has yielded a new, simple method for accurate radiographic determination of RVV in adult man using the equation $V = \frac{\pi}{4} \frac{A_{RAO} \cdot A_{LAO}}{H}$.

ELECTROPHYSIOLOGIC AND PATHOLOGIC CORRELATIONS IN TWO CASES OF CHRONIC 2° AV BLOCK WITH LEFT BUNDLE BRANCH BLOCK

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Previous studies from our laboratory have demonstrated excellent correlations between electrophysiological and pathological findings in patients with intact AV conduction with bundle branch block, and in patients with chronic complete heart block. There have been no such correlative studies to date in the literature in 2° AV block.

The present study concerns 2 cases which had chronic 2° AV block with left bundle branch block (LBBB). Pathologic studies included serial section of the conduction systems. Case one showed type I 2° block with LBBB. Electrophysiological studies revealed 2° AV block proximal to H and a prolonged HV interval (60 msec). Pathologically there was moderate to marked fibrosis of the approaches to AV node and AV node, marked fibrosis of the left bundle branch, and moderate involvement of the right bundle branch. Case two had type II 2° AV block with LBBB. Electrophysiologically the site of block was distal to H, and there was a prolonged A-H interval (145 msec). Pathologically there was marked fibrosis of the AV node and of both bundle branches.

In summary, this study reveals excellent correlation between electrophysiologic and pathologic changes. It also emphasizes that there may be multiple sites of disease and delay in the AV conduction system in an individual patient. In the above patients there was significant disease both proximal and distal to the His bundle, seen both electrophysiologically and pathologically.

TEMPORAL RELATIONSHIP OF LOCAL ELECTROGRAMS AND CONTRACTILE CHANGES FOLLOWING CORONARY OCCLUSION AND REVASCULARIZATION

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To better understand the functional correlate of changes in epicardial ST segments after coronary reperfusion, a simultaneous study of electrographic and local tension changes was undertaken 1 and 3 hr after coronary occlusion and after reperfusion in 15 dogs using epicardial electrograms (10-12 sites) and Walton-Brodie gauges. After occlusion, ischemic zone tension decreased to 58.4 ± 4.4% ($p < .001$), total ST elevation (ΣST) increased from 8.6 ± 2.4 to 62.5 ± 7.2 mv ($p < .001$) and average ST elevation ($\overline{S\text{-}T}$) from 0.7 ± 0.2 to 5.7 ± 0.7 mv ($p < .001$). After 5-10 min of reperfusion 9 studies showed a further fall in tension from 67.3 ± 5.5 to 42.4 ± 6.0 ($p < .001$) concomitant with the appearance of new pathologic Q waves in an average of 5.3 of 8.2 ischemic electrode sites. However, ΣST improved from 66.1 ± 8.2 to 25.9 ± 3.4 mv ($p < .001$) and $\overline{S\text{-}T}$ from 6.4 ± 1.2 to 2.4 ± 0.3 mv ($p < .005$). In 7 studies, tension remained unchanged following reperfusion and no Q waves appeared. However, ΣST again improved from 58.4 ± 12.7 to 27.1 ± 5.7 mv ($p < .025$) and $\overline{S\text{-}T}$ improved from 5.1 ± 1.0 to 2.4 ± 0.4 mv ($p < .025$) within 10 min. When normal saline was distally perfused in 6 studies, similar improvement in ΣST from 68.0 ± 3.6 to 36.3 ± 5.2 mv ($p < .001$) and $\overline{S\text{-}T}$ from 8.1 ± 0.6 to 4.3 ± 0.6 mv ($p < .001$) was observed. Thus, following reperfusion with blood or saline 1 or 3 hr after coronary occlusion, the ST segments markedly improved. However, tension either fails to improve or further deteriorates simultaneous with the appearance of Q waves. Therefore, the ST segment method is of limited value in assessing functional myocardial viability after reperfusion.

EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH AORTIC REGURGITATION USING AFTERLOAD STRESS

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Fourteen patients (pts) with pure aortic regurgitation (AR) were studied by catheterization and quantitative angiography prior to and following afterload elevation with Angiotensin (AT). Resting ejection fraction (EF) was greater than 0.50 in 13/14 pts. AT elevated left ventricular (LV) systolic pressure by 24% (148 to 183 mm/Hg), LV end diastolic pressure by 64% (24.1 to 39.6 mm/Hg), and LV end diastolic volume by 7.7% (271 to 292 ml). Seven of 14 pts maintained their resting EF with AT (Group A), while 7 of 14 experienced a greater than 0.10 decline in EF (Group B). 6/7 A pts showed a rise in LV stroke work indices in response to AT induced elevation of LV end diastolic pressures. In contrast, 6/7 B pts showed flat or declining stroke work indices. This response to AT largely reflected a significant fall in stroke volume in B pts (157 to 115 ml, $p < .01$) compared to a slight rise in A pts (146 to 152 ml, N.S.). 2/7 B pts had relatively small regurgitant fractions (RF) of 0.10 and 0.12 with small LV's and features of restrictive myopathy. The other 5/7 B pts had RF's greater than 0.50 (mean 0.66, range 0.53-0.78), whereas all A pts had RF's less than 0.50 (mean 0.37, range 0.19-0.49). Similarily, these 5 B pts had significantly larger LV end diastolic volumes than did the A pts (Group B - 357 ml; Group A - 251 ml; $p < .05$). We conclude that: 1) Pts with a wide range of severity of AR (RF 0.10 to 0.78) tend to maintain near normal EF's; 2) Some pts with AR exhibit LV dysfunction with afterload stress manifested both by significant decline in EF and by abnormal LV function curves; and 3) Pts who do exhibit LV dysfunction have quantitatively more severe AR with RF's > 0.50.

NITROGLYCERIN-INDUCED IMPROVEMENT IN EXERCISE TOLERANCE AND HEMODYNAMICS IN PATIENTS WITH VALVULAR HEART DISEASE

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Nitroglycerin (TNG) reduces elevated left ventricular filling and pulmonary artery pressures during supine rest in patients with mitral valve disease. To determine whether TNG may prove to be effective therapeutically in ambulatory patients with valvular disease, we evaluated its effects on exercise capacity in 8 severely symptomatic adults. Seven had predominant mitral valve disease; 1 had pure aortic insufficiency. Maximal exercise capacity was assessed by graded treadmill exercise after placebo and after TNG (0.5 mg sublingually) administered in random sequence to each patient. Exercise capacity increased from a mean of 532 sec after placebo to 632 sec after TNG ($p < .005$). To elucidate the hemodynamic determinants of improvement 5 patients were restudied during intense treadmill exercise. Pulmonary arterial pressure was significantly lower ($p < .05$) after TNG than after placebo (mean 45 vs 60 mm Hg). Despite the reduction in pulmonary arterial pressure, cardiac output was higher after TNG (4.5 vs 4.2 L/min, $p < .005$). We conclude that TNG increases exercise tolerance and improves the hemodynamic response to exercise in patients with valvular disease. These results suggest that TNG may be valuable in the long-term pharmacologic therapy of such patients.

NORMAL BAROREFLEX SENSITIVITY IN EXPERIMENTAL COARCTATION OF THE AORTA.

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Baroreflex sensitivity (BRS) is diminished in renal and essential hypertension (HT), but has not been assessed in coarctation (C). Previous experimental studies of C have dealt primarily with renal mechanisms of HT, and have relied on constricting the aorta in adult animals. This may account for their conflicting findings, since natural C is present from birth. We banded the thoracic aorta in newborn puppies, and performed studies 2 years later. Blood pressure (BP) elevations, abundant chest wall collaterals, the absence of heart failure, and subsequent necropsy confirmed the full syndrome of natural C in all dogs. Transient BP elevations were induced in conscious, unrestrained dogs with IV phenylephrine injections. Reflex bradycardia was quantitated by plotting each pulse interval in msec. against BP of the preceding beat, and expressing BRS as the linear regression coefficient (slope) in msec/mm Hg. Mean BRS in 10 dogs with C did not differ significantly ($p > .05$) from 8 normal controls (19.5 vs. 25.3). (Unchanged "sensitivity" in this context must be differentiated from "resetting" to a higher BP.) Carotid sinus lumen diameter (CSLD) was also assessed. Carotid arteries were fixed in vivo by prolonged exposure to glutaraldehyde to prevent contraction, then were excised and measured in a calibrated microscope. Mean CSLD in 10 dogs with C was significantly greater ($p < .05$) than in 10 control dogs (3026 microns vs. 1872 microns).

Diminished BRS does not contribute to HT in C. The unexpectedly normal BRS in C may be due to changes in CSLD induced by HT. Such changes may only develop in growing animals. Experimental studies of C should use a preparation that closely mimics the natural lesion.

NON-INVASIVE QUANTITATION OF MYOCARDIAL INFARCTION WITH ^{99m}Tc(Sn) PYROPHOSPHATE: CORRELATION BETWEEN CREATINE PHOSPHOKINASE DEPLETION AND RADIONUCLIDE UPTAKE.

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To assess infarct size non-invasively, discrete infarcts were created in 6 closed-chest dogs by placement of occlusive catheter plugs in branches of the left coronary artery during fluoroscopy. Scintiphotographs were taken 48 hours post-occlusion (1-2 hrs. after IV injection of 15 mCi ^{99m}Tc(Sn) pyrophosphate) using a scintillation camera interfaced to a small digital computer. Clear images of each infarct were obtained which correlated well with ECG localization (4 anterior, 2 inferior) and the site of occlusion. Following sacrifice the intact and opened hearts were also imaged in vitro. Biopsies of infarcted, borderline, and normal tissue were analyzed for radioactivity, creatine phosphokinase (CPK) content, and histology. Significant radioactivity was found only in regions of histologically confirmed infarction. There was a good correlation between infarct size and uptake of radioactivity in vivo and in vitro. There was also a good inverse relationship between radioactivity (CPM) and CPK content (CPK_c) such that $CPM = -2400\ CPK_c + 65800$ ($r = 0.79$, $P < 0.001$) where CPM is in cpm/mgm protein and CPK_c is in IU CPK/mgm protein. In conclusion, ^{99m}Tc(Sn) pyrophosphate localized specifically in areas of infarcted myocardium in amounts proportional to the degree of CPK depletion. This imaging technique provided in vivo and in vitro quantitation of infarct size. This study provides strong support for the clinical application of this technique in the detection and quantitation of acute myocardial infarction.

MODIFICATION OF ACUTE MYOCARDIAL INFARCTION SIZE WITH LIDOCAINE IN DOGS.

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The antiarrhythmic effect of Lidocaine (L) in acute myocardial infarction (AMI) is well established. However the effect of L on AMI size is not well known. AMI was produced in 30 dogs by ligation of anterior descending coronary artery. Epicardial mapping was performed before and every 10 minutes (min.) for 150 min. after the AMI. The average ST segment elevation (ΣST) and the number of sites showing this elevation (more than 2 mV) (NST) were assessed and were used as an index of AMI size. The dogs were divided into 3 groups: (A,B,C). A, 10 control dogs. B, 10 dogs were given a bolus of 100 mg L IV. C, 10 dogs were given the same bolus injection of L and an infusion of 2 mg/min. for 120 min. Blood pressure, central venous pressure, and heart rate were unchanged during the study. In A, the ΣST and NST were the same 30 min. and 150 min. post AMI. In B, the ΣST was 123±19 in 30 min. post AMI and 65±16 in 150 min. post AMI or 120 min. post L, ($P<0.001$). The NST at the same time was 12.8±1.5 and 9.6±1.8 respectively, ($P<0.025$). In C, the ΣST was 166±30 in 30 min. post AMI, and 77±14 in 150 min. post AMI or 120 min. post L, ($P<0.001$). The NST at the same time was 13.8±1.9 and 10.1±1.9 respectively ($P<0.025$). L reduced significantly the AMI size. There was no difference in ΣST and NST changes between B and C. Preliminary data from 6 of our patients with AMI revealed that L had a similar effect on ΣST and NST. These changes may be explained by the slight negative inotropic effect which L is known to have, although other effects can not be excluded. It is hypothesized that L has decreased the mortality of AMI not only because of its antiarrhythmic effect but also because of its effect on AMI size.

COMBINED HEMODYNAMIC-ULTRASONIC METHOD FOR STUDYING LEFT VENTRICULAR WALL STRESS: COMPARISON WITH ANGIOGRAPHY.

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Left ventricular (LV) wall stress is an important parameter of cardiac function at the myocardial level. Its calculation in man has traditionally required angiographic and LV pressure (P) measurement, making study of interventions difficult. We have developed a combined hemodynamic-ultrasonic technique for measuring LV meridional wall stress (σ_m) throughout the cardiac cycle. Simultaneous measurement of LVP, ultrasonically determined wall thickness(h_{echo}), and minor axis(D_{echo})were made during cardiac catheterization in 3 patients each with normal LV function, LV pressure overload, and LV volume overload. Within 30 minutes, LV cineangiography was performed in each subject and angiographic wall thickness(h_{angio})and minor axis(D_{angio})calculated. Comparison of values for each subject throughout the cardiac cycle (average 19 data points/cycle) yielded close correlation; for D_{echo} vs D_{angio}, r values ranged from .82 to .98 and averaged .91, while for h_{echo} vs h_{angio} r values ranged from .56 to .98, averaging .81 for the 9 subjects. σ_m was calculated after Sandler and Dodge as $PR_i^2/h(2R_i+h)$, where R_i=inner wall radius, calculated as D/2 for both echo and angio methods. Agreement between ultrasonic and angiographic methods was excellent in each subject, with close superimposition of the stress-time plots constructed by the different techniques.

In summary, a new method for measurement of LV wall stress has been developed and validated by comparison to an angiographic reference standard. This method has potential advantages, including the ability to study σ_m continuously and assess its response to serial interventions.

SEQUENTIAL REGIONAL TISSUE BIOPSY AND MYOCARDIAL METABOLISM FOLLOWING CORONARY OCCLUSION AND REPERFUSION

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Histochemical (H) glycogen (G) of endocardial (EN) and epicardial (EP) biopsies (B) from ischemic (I) and non-ischemic (NI) segments of the left ventricle provided a characterization of alterations following LAD coronary artery occlusion (O). The H determinations were related to simultaneously measured myocardial tissue and arteriovenous potassium (K) and CPK balances, as well as to hemodynamics and ECG measurements.

A new B needle (Travenol Tru-Cut) exhibited minimal trauma and provided intact transmural tissue cylinders suitable for analysis at different depths of the myocardial wall. Control B was performed in 4 dogs over a period up to 5 hours. In another 9 dogs, following control (C) the proximal LAD was occluded for up to 5 hours, and sequential simultaneous samples were taken from the anterior (O) and posterior (NO) zones of the LV. G of EN and EP were analyzed by a double blind test and are expressed semiquantitavely between 4+ (normal) and 0:

		C	15'-O	1 Hr-O	2 Hr-O	5 Hr-O
NO		4+	4+	3.5+	3+	4+
O	EP	4+	2+	1.5+	1.5+	1.5+
	EN	4+	0.5+	0.5+	0.5+	1.5+

In 2 dogs, 3 hour LAD O was followed by 2 hours reperfusion (R) which exhibited a return of glycogen from 1+ (O) to 3+ (R). Tissue CPK and K corresponded generally to (A-V) myocardial balances throughout the occlusion period. These experiments indicate that H-G is an early and sensitive index of ischemic derangements. G provides an end point for evaluation of effectiveness of reperusion or other interventions.

PREVALENCE OF AORTIC ROOT DILATION AND MITRAL VALVE PROLAPSE IN MARFAN"S SYNDROME: AN ECHOCARDIOGRAPHIC STUDY.

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Cardiac abnormalities were assessed by echocardiogram and phonocardiogram in 35 patients with Marfan's Syndrome. Arachnodactyly and a positive family history of Marfan's were present in all patients. Ocular abnormalities were present in 28 of the patients.

Echocardiography revealed aortic root dilation and/or mitral valve prolapse in 34 of the 35 patients. Aortic root dilation was found in 21 (60%) patients and was most common in males (17/23 males, 4/12 females). Mitral prolapse was present in 31 of the 35 patients studied (20/23 males, 12/12 females). Incidence of aortic dilation and mitral prolapse was essentially equal in children and adults of the same sex.

Auscultatory examination revealed abnormalities in only 19 of the 35 patients (54%). A murmur of aortic regurgitation was found in 8 of 23 males (35%),but in no females. Incidence of aortic regurgitation was much higher in adult males (7/14) than male children (1/9). A murmur of mitral regurgitation and/or a mitral click were found in 16 patients (9/23 males, 7/12 females). The incidence of abnormal mitral sounds was essentially the same in adults and children of the same sex.

Cardiac abnormalities are a more consistent manifestation of Marfan's than previously suspected and, with an appropriate family history, are as helpful diagnostically as skeletal or ocular abnormalities. Mitral prolapse and aortic dilation often occur in these patients without abnormal auscultatory findings, indicating ultrasound as the more appropriate screening tool. Aortic dilation may be progressive in males, and therefore of prognostic clinical significance. Mitral prolapse is commonly found in these patients, which may imply susceptibility to bacterial endocarditis.

PHYSIOLOGIC EVALUATION OF THE INDICATIONS FOR SURGICAL CLOSURE OF CORONARY ARTERIOVENOUS FISTULA

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Surgical closure of coronary arteriovenous fistulae is recommended if 1)"coronary steal" can be demonstrated angiographically, and 2) a significant shunt can be detected from catheterization data. This study tests the hypothesis that neither criteria must be satisfied for a small shunt (10-15% of cardiac output) to cause ischemia. In 7 anesthetized dogs, we produced a coronary arteriovenous fistula (vein graft) from left anterior descending (LAD) coronary artery to the right atrium. Blood pressures were measured in left ventricle (LV), aorta, and coronary artery. We measured flow through the shunt and distal LAD (flowmeter), and nutritive myocardial flow (radioactive microspheres, 8-10 μ) in the vascular bed supplied by the LAD (apex) and circumflex coronary arteries (base), during a) control conditions, b) with the shunt open, and c) after raising cardiac O_2 requirements by atrial pacing. Opening the fistula (200-300 cc/min) caused no significant change in heart rate or systemic blood pressure, but reduced perfusion pressure in the distal LAD by 41 mm Hg ($p<.01$). Flow through the LAD decreased 36% ($p<.01$). However, nutritive flow to the LV apex decreased only 16% ($p<.01$) while flow to the base of the heart did not change. Reversed flow never occurred (no coronary steal). When myocardial oxygen demands were raised by pacing (shunt open), nutritive flow to the apex fell 27% ($p<.01$) below control values while flow to the base of the heart increased 15% ($p<.01$). Coronary steal did not occur. We conclude that even when coronary arteriovenous fistula causes no significant systemic hemodynamic changes or coronary steal, it may cause focal myocardial ischemia.

MYOCARDIAL LESIONS OF PROGRESSIVE SYSTEMIC SCLEROSIS: A CAUSE OF CARDIAC DYSFUNCTION.

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The nature and functional significance of the cardiac lesions of progressive systemic sclerosis (PSS) are uncertain. Clinical and pathologic features of 52 necropsy patients (pts) with PSS were reviewed. Focal myocardial ischemic lesions ranging from muscle cell necrosis to fibrosis scattered randomly throughout both ventricular walls appeared characteristic of PSS. No significant occlusive lesions of intramyocardial coronary arteries were demonstrated by histology (52 pts) or microangiography (12 pts). Serial sections of conduction systems in 25 pts showed no consistent abnormalities which correlated with electrocardiographic (EKG) evidence of conduction block.

Of the 48 pts with normal extramural coronary arteries, myocardial lesions of PSS were severe in 11, mild in 10 and absent in 27. The 3 groups were similar as to age, sex, and frequency and severity of kidney and lung involvement by PSS. Systemic hypertension was present in 24 of 48 pts, but in none of the 11 with severe myocardial lesions. Eight of 9 pts with ventricular irritability (premature ventricular contractions) had severe PSS lesions and 2 of them died suddenly. In 2 pts with no kidney or lung disease severe congestive heart failure was attributable to extensive myocardial fibrosis. Angina pectoris with documented ischemic EKG changes was present in 3 pts with normal coronary arteries and severe myocardial scars.

PSS heart disease may cause congestive heart failure, angina pectoris with normal coronary arteries, ventricular irritability and sudden death. It is suggested that these findings can be attributed to a cardiac Raynaud's phenomenon.

EFFECT OF STIMULUS SITE IN RELATION TO LESION ON MEASURED VENTRICULAR FIBRILLATION THRESHOLD

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The effect of site of test stimuli in relation to lesion on measured ventricular fibrillation threshold (FT) was studied in dogs after 2 minutes of coronary occlusion (CO), and in dogs with localized alterations in recovery properties induced with thermal lesions. In the latter group refractory periods (RP) and activation times (AT) were measured at sites adjacent to FT test sites. The atria were driven at fixed cycles of 330 to 500 msec. FT was measured at sites within or adjacent to (M), and distant (D) from the lesions with 200 msec duration trains of 100 Hz, 5 msec duration stimuli. In all 8 CO experiments, FT measured at M fell by an average of 30% of control values. FT measured at D fell in 4 cases and increased in 4 cases, with an average decrease of 7%. In dogs with thermal lesions, RP and AT were used to estimate disparity in time of recovery occurring with drive from each FT test site. The greatest decrease in FT occurred with test sites that produced the greatest disparity in time of recovery. When recovery times were shortened FT measured at M fell in 6 of 6 experiments with an average decrease of 71%. FT measured at D increased in 4 of 6 by an average of 2%. When recovery times were prolonged, FT measured at both D and M fell. In 7 of 12 experiments FT measured at D fell more than FT measured at M. FT decreased by an average of 53% at D, and by an average of 49% at M. The findings indicate that measured FT is dependent not only on underlying electrophysiologic properties, but also on site of application of test stimuli. FT values are more dependent on stimulus sites with lesions that have short recovery times than with lesions with long recovery and conduction times. Test sites producing the maximal disparity in time of recovery are associated with the lowest measured FT.

COMPARATIVE EFFECTS OF LIDOCAINE AND PROCAINAMIDE ON ACUTELY IMPAIRED HEMODYNAMICS.

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Controversy exists about the relative safety of lidocaine (Ld) and procainamide (P) in patients (pts) with acutely impaired hemodynamics. Accordingly, their effects were studied in 11 such pts, 10 with acute myocardial infarction and 1 with cardiomyopathy and acute pulmonary edema. All had elevation of pulmonary capillary wedge pressure (PCW) >15 mmHg and/or low cardiac index (CI) <2.5 L/min/m^2. The study protocol consisted of a 100 mg bolus of Ld followed by a 3 mg/min infusion during which measurements were made early at 5 minutes (e) and late at 20 minutes (l). Following at least a 30 minute recovery period, a 100 mg bolus of P was given followed by a 20 mg/min infusion with hemodynamic measurements at similar times. The accompanying table displays the mean data ±SEM and consists of heart rate (HR) in beats/min, mean PCW in mmHg, mean arterial pressure (MAP) in mmHg, CI in L/min/m^2, and total peripheral resistance (TPR) in resistance units.

	HR	PCW	MAP	CI	TPR
Control (i)	82±6	20±3	88±5	2.6±.2	18±2
Ld (e)	86±6	22±2	90±6	2.5±.2	20±2
Ld (l)	84±6	22±2	92±6	2.5±.2	20±1
Control (ii)	82±5	20±3	88±6	2.6±.2	18±2
P (e)	83±6	19±2	85±5	2.6±.2	18±1
P (l)	86±5	19±2	85±5	2.6±.2	18±1

No value significantly different from control ($p>0.05$).

These data suggest that in pts. with acutely impaired cardiac function, either lidocaine or procainamide may be used without producing hemodynamic deterioration.

SYSTEMIC HYPEROSMOLALITY WITH VIGOROUS GRADED EXERCISE: A DETERMINANT OF HEMODYNAMIC RESPONSE

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The hemodynamic response to vigorous exercise shows marked individual variation. Recent work from our laboratory has indicated that abrupt increases in plasma osmolality (Posm) may result in significant falls in systemic blood pressure by reflex and direct mechanisms. To test the possibility that osmotically active substances released from muscle might alter systemic Posm sufficiently to contribute to variation in exercise hemodynamics, 25 healthy adults (mean age 26.4 years) underwent a standard graded treadmill exercise test (Bruce protocol). Blood pressure (BP) and Posm of arm venous blood was obtained at each stage and at peak exercise.

Pre-exercise Posm was 291.5±0.9 mosm/kg (mean±SE). The mean exercise duration time was 13.8 min. (range: 9.0 to 18.0). During exercise, a progressive increase in Posm occurred at each stage (2.0±0.5 at Stage I to 17.7±1.1 at Stage V). At peak exercise, increases in Posm ranged from 8 to 29. The BP response at peak exercise was variable: mean BP rose in 12 and fell or was unchanged in 9 (range -33 to +37 mmHg). Of those subjects with only modest increases in Posm (<20 mosm/kg), 10 of 11 had elevated mean BP at peak exercise (mean +14.5±3.9 mmHg, range -11 to +37); whereas 8 of 10 subjects with marked increases in Posm (>20 mosm/kg) demonstrated a fall or no change in mean BP at peak (mean -4.0±4.4, range -33 to +18) ($p<.01$).

Thus systemic hyperosmolality occurs during vigorous graded exercise. The extent to which Posm rises appears to be a factor in the BP response and may in part contribute to the individual hemodynamic variability observed.

IDIOPATHIC PAROXYSMAL VENTRICULAR TACHYCARDIA IN NORMAL HEARTS: INTRACARDIAC ELECTRICAL, HEMODYNAMIC AND ANGIOGRAPHIC OBSERVATIONS AND ASSESSMENT OF THERAPY

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In 6 patients with idiopathic paroxysmal ventricular tachycardia (PVT), His bundle electrography verified right ventricular origin in 4 and left in 2. Response to atrial pacing was normal. Four had intermittent type 1 and 2 had sustained type 2 PVT. In 4 with type 1 the vectorcardiogram was normal; 2 with type 2 showed S_1 S_2 S_3 and terminal QRS loop delay. Three over age 40 years had syncope; 3 under age 25 had no syncope despite more prolonged bouts of PVT. All achieved NYHA Class I on treadmill exercise; 3 had significantly less rise in systolic pressure than predicted ($p< 0.05$); 3 overdrove the dysrhythmia at sinus rates of 126-183% of control. At catheterization, normal hemodynamics and coronary angiograms were seen in 6. Left ventricular (LV) cineangiography, performed in 5, showed normal LV, mitral valve and LV ejection fraction. All patients are well. Mean follow-up from ECG diagnosis is 2.9 (0.5-8.0) years. One with type 2 PVT had no recurrence in 6 months on no medication; 1 with type 1 PVT had no recurrence off coffee and tobacco without medication. In 3, diphenylhydantoin 4.2-8.0 and propranolol 0.8-2.7 mg/kg/day controlled PVT. This combination yielded superior PVT control without side effects compared to quinidine and procainamide. In 1 followed elsewhere, propranolol 0.5 and procainamide 22.0 mg/kg/day abolished PVT, but not ventricular ectopy. Combined propranolol and diphenylhydantoin is the drug regimen of choice in idiopathic PVT.

CORONARY ARTERY LESIONS ASSOCIATED WITH UNSTABLE ANGINA

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15-40% of the cases of unstable angina (UA) develop an acute myocardial infarct (AMI). This study was undertaken to determine whether any morphologic alteration in coronary arteries is associated with UA. The major coronary arteries from 40 autopsied patients (pts) were perfused, fixed and sectioned at 2 mm intervals. Light microscopic slides were prepared of each plaque. The 40 pts consisted of 11 with no symptoms of coronary artery disease, 10 pts with AMI and UA, 10 with AMI without preceding UA and 9 consecutive AMI pts examined before reference to antecedent history. Thirty-three morphologic criteria were evaluated as either present or absent, or graded 0-3+ when appropriate. These data were transferred to tape and a computer used to print out the data in various configurations.

Thirteen of 15 pts with UA had multiple plaque hemorrhages in 2 or more epicardial arteries and occlusive thrombosis at the site of infarction. The hemorrhages were of variable age as evidenced by red cell lysis, hemosiderin deposition, and varying amounts of granulation tissue. In 12 pts with AMI without preceding UA 11 showed a single hemorrhage at the site of arterial thrombosis. Only one pt had plaque hemorrhage in 2 epicardial arteries. In the 11 control pts 2 small hemorrhages were found. The anatomic change common to all of these pts with AMI is plaque hemorrhage with thrombosis. The UA pts were differentiated by the presence of multiple hemorrhages of varying ages in 2 or more arteries suggesting an ongoing process that culminated with a plaque hemorrhage, overlying thrombus formation and infarction.

CHRONOTROPIC INCOMPETENCE IN EXERCISE TESTING

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Chronotropic incompetence upon exercise, defined as pulse rate for achieved workloads below the 95% confidence limits of the established normals for age and sex was studied in 49 patients with maximal stress testing and heart catheterization. 23 exhibited a pulse rate response 2 SD below the predicted mean. 16 showed ST segment depression whereas 7 had normal ST segments. 5 of these 7, however, had coronary obstruction of more than 50% and the other 2 had elevated LVEDP at rest. 10 of the ischemic responders had severe 3 vessel coronary disease, 2 had 2 vessel disease, 2 had 1 vessel disease and 2 had elevated LVEDP at rest.

The other 26 subjects demonstrated a pulse rate response below one SD. 18 showed normal ST segments and 8 had ST segment depression. 6 of the normal ST responders had significant disease whereas all 8 ischemic responders showed disease. In 2700 subjects subjected to maximum stress testing, there was a 40% incidence of coronary events in 4 years among 85 patients with chronotropic incompetence and normal ST segments compared to a 6% incidence among 1067 patients with normal chronotropic response and ST segments.

A slow pulse rate response to exercise, even in absence of ST segment depression, may be a reliable index for coronary artery disease or LV dysfunction.

EFFECT OF PROPRANOLOL ON MYOCARDIAL GLYCOGEN STORES AND HEMODYNAMIC PERFORMANCE DURING ANOXIA

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Glycogen is an essential substrate during myocardial anoxia. Since propranolol (P) may maintain myocardial glycogen levels after acute stress by blockade of catecholamine induced glycogenolysis, we evaluated the effect of P treatment in the isolated perfused isovolumic paced rat heart. Forty rats were studied after 10 min of ice water immersion: half were pre-treated with P 20/mg/kg/day x 3 and half with saline(controls (C)). Glycogen content of unperfused P treated hearts exceeded C by 44%(146±9 vs 101±5umol/gdw,p<.02) and this difference persisted during aerobic perfusion. P did not affect adenine nucleotide concentrations or left ventricular (LV) hemodynamics. Following 5 min of anoxic perfusion,P hearts showed improved ventricular performance concomitant with enhanced glycogenolytic flux and lactate production:

	LVSP (mmHg)	dP/dt (mmHg/sec)	LVEDP (mmHg)	$\dot{Q}$ Glycogen (umol/gdw)	Lactate (umol/min)
P)	46±1	733±45	10±2	82	8.30±.71
C)	37±2	416±39	18±2	63	5.82±.45

Differences are highly significant.P augmented high energy phosphate production (ATP/AMP=5.2±0.4 vs. 3.4±0.5,p<.02) and increased coronary flow (22±2 vs. 17±1 ml/min,p<.02) during anoxia. Thus, P supported glycogen stores during acute stress; during subsequent anoxia, P enhanced glycogenolytic energy production, increased coronary flow and improved ventricular function.

SHOULD THE SINUS VENOSUS TYPE ASD BE CLOSED? A REVIEW OF THE ATRIAL CONDUCTION DEFECTS AND SURGICAL RESULTS IN TWENTY EIGHT CHILDREN.

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Twenty eight patients with sinus venosus atrial septal defects(SV) confirmed at surgery and followed for at least 1 year were analysed for evidence of sinus node dysfunction(SND) and operative results. SND was diagnosed by ectopic atrial focus (p wave axis less than 0^{o}), varying p wave morphology; or absent p wave and junctional rhythm. Review of postoperative cardiac catheterization(PCC) was done to assess the adequacy of surgical repair. The results were compared with 68 cases of ostium secundum(OS) that were closed during the same period. Preoperative SND was found in 5 (18%) of the SV group and postoperatively in 14 (50%) compared with 3 (4%) and 21(31%) respectively of the OS. Nineteen(70%) of the SV had sinus node dysfunction compared to 24(36%)of the OS. These changes were transient in 3 (10%) of the SV as compared to 10(15%) in the OS group. PCC of the OS patients showed 100% closure rate irrespective of the type of closure. Ten SV patients had PCC and 6 had residual defects, two with critical obstruction of the superior vena cava and 4 had persistent shunts. The greater frequency of pre-op sinus node dysfunction is a useful sign in diagnosing the sinus venosus type ASD. The post-op incidence of permanent SND is much higher compared to the OS group. There is also a high incidence of failure of complete surgical repair in SV compared to OS. These postoperative findings should be weighed against the natural history of the lesion when one recommends closure of the SV ASD.

THE ANGIOGRAPHIC DEMONSTRATION OF CORONARY ARTERY SPASM IN PATIENTS WITH SUSPECTED VARIANT ANGINA: METHOD AND THERAPEUTIC IMPLICATIONS.

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A specific method to precisely document the occurrence and location of coronary artery spasm in patients (pts.) with clinically suspected variant angina pectoris is of utmost diagnostic and prognostic importance. Spontaneous spasm with pain and ischemic EKG changes has been demonstrated during angiography in several pts. The induction of coronary spasm by the intravascular administration of a known vasoconstrictor, ergotamine tartrate (E.T.), has been attempted in 40 pts. Severe focal as well as diffuse coronary artery spasm has been demonstrated in 8 pts. The focal lesions have been at the sites of mild atherosclerotic lesions. Total occlusions of right and anterior descending coronary arteries have been induced. The effects of E.T. are promptly and reliably reversed by nitroglycerin. No complications have occurred. The administration of E.T. during coronary angiography is a safe procedure which precisely documents coronary spasm. The choice between medical or surgical management has been dependent on the localization and severity of the spasm.

INFECTION CONTROL IN CARDIAC SURGERY

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Prosthetic valve infection continues to carry a high mortality. This report is an analysis of four years of experience in which multiple concomitant techniques were used to decrease infection rates. Between September 1, 1970 and August 30, 1974, 332 patients received 416 prosthetic valves. 279 patients were at risk of valve infection seven or more days after operation. Four major measures were used to achieve these results: (1) special attention to frequent prosthetic valve sterilization and enclosure until immediately prior to use, (2) vertical high flow unidirectional ventilation with HEPA filtration, (3) creation of awareness of the problem by an active bacteriologic monitoring program, and (4) careful preoperative patient skin preparation of the personnel. The results show that three or 1.07% of the 279 patients at risk developed prosthetic valve infections. One has survived. The combined superficial and deep wound rate is 2.5%. It is concluded that frequent sterilization of heart valves, minimal exposure times in a clean atmosphere where the airborne bacterial concentration is ≤ 0.5/cu.ft. at the wound, impervious low lint drapes, monitoring of the hands, nose and throats of both scrubbed and unscrubbed personnel and effective bacteriologic control of patient skin flora has resulted in a low prosthetic valve infection rate compared to reports of others.

THE CARDIOVASCULAR IMPLICATIONS OF RETINAL ARTERY OCCLUSION

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Thrombosis has previously been accepted as the etiology of retinal artery occlusion (RAO). The validity of this concept was tested by a prospective multidisciplinary clinical study of 25 cases of RAO. 18 cases were caused by embolism, and only 7 cases were attributed to thrombosis. Funduscopic examination revealed definite embolic material (calcium, cholesterol or platelet plug) in 9. Probable emboli were diagnosed in 9 others by a history or prior embolism and the identification of a potential source of embolic material. The emboli arose from previously unrecognized carotid artery stenosis (CAS) in 12, calcific aortic valve stenosis (CAVS) in 4 and both CAS and CAVS in 2. CAS angiograms showed unilateral carotid atherosclerotic disease in 6 and bilateral disease in 4; 8 had severe and 2 had mild stenotic lesions; 2 had ulcerated atherosclerotic plaques. CAVS patients showed little evidence of congestive heart failure, syncope or angina, but 3 had prior (?embolic) myocardial infarctions. 21 RAO patients had atherosclerotic risk factors, and 11 had one or more manifestations of systemic vascular disease. 8 patients developed new systemic vascular complications during the average 9 month follow-up period; 2 of these were embolic. In summary, RAO is not merely an ocular problem. Most RAO are due to embolism rather than thrombosis. RAO is a presenting sign of previously unrecognized CAS or CAVS, and it is a warning of impending vascular accidents.

SURGICAL MANAGEMENT OF INTERRUPTED AORTIC ARCH

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The five year experience of the New England Regional Infant Cardiac Program in twenty-nine patients with interrupted aortic arch (IAA) was reviewed. Twelve infants were Type A (preductile interruption), nine were Type B (left common carotid-left subclavian artery interruption), five were Type C (right innominate-left common carotid artery interruption), and three were not classified. All had major associated cardiac abnormalities: patent ductus arteriosus, twenty-seven; ventricular septal defect (VSD), twenty-two; hypoplastic left heart, eight; d-transposition of the great arteries (d-TGA), three; single ventricle, three. Seventy-nine percent (23/29) underwent surgery; all operated patients had patent ductus arteriosus ligations. Nine of these had additional palliative operations: three, simple pulmonary artery banding (PAB), and six, combined PAB and pulmonary artery to descending aorta grafts (PAG). Three have survived surgery for at least three years. Aortic arch reconstruction was undertaken in fourteen patients, one of whom had been previously palliated (PAB and PAG), with three alive at ages 4 months (2), and 4 years (1). All three, however, continue to have congestive heart failure, recurrent pulmonary infections, and growth failure. Six of the twenty-nine patients did not have surgery, five of whom died before ten days of age. One with d-TGA and VSD is alive at four years of age. Although various procedures have been tried in these very ill neonates, our expereince suggests that both palliative and reconstructive operations are less than optimal in achieving satisfactory clinical results.

ELIMINATION OF THE NEED FOR ANTICOAGULATION FOLLOWING MITRAL VALVE REPLACEMENT

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Patients with chronic atrial fibrillation and enlarged left atria represent a high risk group for thromboembolism after mitral valve replacement (MVR). The Hancock porcine valve, stabilized with glutaraldehyde, has been used in 91 patients for mitral, aortic and multiple valve replacement with a 2% operative mortality and 3.5% late mortality. The incidence of thromboembolism was 1/91 (1%) without anticoagulation.

Thirty patients with chronic atrial fibrillation under went MVR and have been followed from 4 to 33 months, 16.2. There was a zero incidence of postoperative thromboemboli in this group despite no anticoagulation after an initial 6-week postoperative course of wafarin. The total number of embolus-free patient months was 486.

The Hancock porcine mitral valve should be considered for patients with a high risk of thromboembolism particularly if they have been in chronic atrial fibrillation.

THE PROTECTIVE EFFECTS OF NITROGLYCERIN ON ISOMETRIC EXERCISE

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Isometric exercise is an every day activity often overlooked as a cardiovascular stress. To determine the influence of nitroglycerin(TNG) on the cardiovascular response to isometric exercise, 9 pts performed 30% handgrip (HGP) before and 4 min. after 0.4 mg TNG sublingually, at the time of cardiac catheterization. The increment in left ventricular systolic pressure(LVSP)and HR during HGP was similar before and after TNG. However, since TNG decreased the resting LVSP and accelerated the resting HR, during HGP absolute value for LVSP was significantly lower and the HR significantly faster. The increment in LVEDP during HGP was likewise similar before and after TNG. The resting LVEDP decreased significantly from 17 mmHg to 5 mmHg ($p<0.05$) following TNG and rose to a significantly lower level during HGP(mean value of 12 mmHg with TNG compared to a mean value of 22 mmHg prior to TNG) ($p<0.02$). Neither CI nor LVSWI changed significantly during HGP prior to TNG. Following TNG, both parameters decreased significantly at rest (C.I. = 1.97 L/min/M^2, LVSWI = 43 gm-M/beat/M^2)and rose to pre TNG levels during HGP (C.I. = 2.71 L/min/M^2, LVSMI = 55 gm-M/beat/M^2).

While TNG does not alter the pressor or chronotropic effects of HGP, it does permit patients to engage in a given isometric effort at a significantly lower LVEDP and systemic pressure. These decreases in preload and after load clearly benefit the patient with coronary artery disease.

UNSTABLE ANGINA PECTORIS: RANDOMIZED STUDY OF SURGICAL VS. MEDICAL THERAPY.

National Cooperative Unstable Angina Pectoris Study Group

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A cooperative prospective randomized study of maximal medical vs. surgical therapy in patients (pts.) with unstable angina pectoris (UAP) was started in 1972. UAP was defined as angina of recent onset or crescendo nature (usually with rest pain) associated with transient ST-T wave changes and no evidence of myocardial infarction (MI). Angiographic criteria required >80% narrowing of distal vessels and a reasonably functioning left ventricle (ejection fraction-EF->30%). Randomization occurred after anatomy was judged suitable for vein bypass.

Of the first 138 randomized patients 73 received medical and 65, surgical therapy. Analysis of EF, end diastolic pressure, age, number of vessels involved, arrhythmias, ST directional changes, previous MI and previous stable angina showed the 2 groups to be evenly matched and that none of these factors predicted a superior mode of therapy. There were 4 surgical (3 peri- and 1 postoperative) and 2 medical inhospital deaths. After a mean follow up of 7 months there were 2 surgical and 3 medical late deaths. Surgical patients evolved 14 inhospital MI's (3 pre-, 9 peri-, 2 postoperative) and 5 late MI's. Medical patients had fewer ($p<.05$) MI's with 6 inhospital and 5 late MI's. However, medical pts. had a higher incidence of angina Class II-IV at last follow up ($p<.01$). Thus, preliminary data with a short follow up suggests an equal mortality, a higher surgical MI rate but a higher medical angina rate. Final conclusions must await a longer follow up.

OCCLUSION SITE AS A DETERMINANT OF THE DELETERIOUS EFFECTS OF ATROPINE IN EXPERIMENTAL MYOCARDIAL INFARCTION

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The use of atropine in clinical myocardial infarction is currently controversial. In chloralose-anesthetized cats, we have previously demonstrated that atropine pretreatment increases the incidence of fatal ventricular arrhythmias induced by left anterior descending coronary artery (LAD) occlusion. The purpose of the present study was to determine whether this deleterious effect of atropine also applies to arrhythmias produced by right coronary artery (RCA) occlusion. Ligation of the RCA resulted in ventricular arrhythmias in all 20 animals studied, followed by ventricular fibrillation (VF) in 3 animals (15%). RCA occlusion also resulted in bradycardia (-30.2 ± 5.1 bpm) and hypotension (-23.2 ± 4.9 mmHg). Atropine-pretreatment of 15 animals caused no significant increase in the incidence of VF (20%). Indeed, there was a significant reduction in the number of animals developing ventricular arrhythmias. Atropine-pretreatment also significantly antagonized the fall in heart rate (-19.7 ± 6.6 bpm), but did not affect the hypotension (-17.5 ± 4.8 mmHg) associated with RCA ligation. Sectioning the vagus nerves produced results identical to atropine pretreatment. Therefore, the increased mortality after atropine in experimental LAD occlusion is not demonstrated with RCA ligation. These results indicate that the potential for deleterious effects of atropine in acute infarction might depend on the anatomic location of the involved myocardium.

RIGHT VENTRICULAR VOLUME CHARACTERISTICS IN TETRALOGY OF FALLOT

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Although treatment for suspected right ventricular (RV) failure is common after tetralogy of Fallot (T/F) repair, very little information is available on the direct measurement of RV performance in these patients. Accordingly, biplane cineangiocardiograms were analyzed in 23 preoperative pts. (ages 5 weeks to 6 yr), 10 postshunt pts. (ages 1.7 to 14 yr) and 11 postrepair T/F pts. (ages 1.6 to 10.8 yr) to determine RV end-diastolic volume (EDV), ejection fraction (EF), systolic output (SO), and maximal right atrial volume. RVEDV averaged 96 ± 4% ($\bar{x}$ ± SEM) of normal ($p > 0.05$) in all preop patients but RVEF was mildly depressed 0.59 ± 0.02 vs. a normal value of 0.65 ± 0.01 ($p < 0.008$) as was RVSO (84 ± 6%, $p < 0.02$). Postshunt patients also showed normal RVEDVs (106 ± 5%, $p > 0.5$), mild depression of RVEF (0.55 ± .02, $p < 0.001$), but normal RVSO (91 ± 6%, $p > 0.1$). Five of 11 postrepair pts. showed increased RVEDVs (137-262% of normal) and all five had pulmonary insufficiency. RVEF was decreased to < 0.50 in five of 11 pts. and the average value for the entire group was depressed (0.52 ± 0.03, $p < .001$). RVSO was within normal limits for the postop group (110 ± 13%, $p > 0.3$). All pt. groups showed elevated right atrial volumes. Postoperative abnormalities of RV function may be related to outflow tract dyskinesis and/or pulmonary insufficiency caused by the ventriculotomy and/or outflow tract patch required for repair of the more severe T/F patient.

COMPARISON OF ULTRASOUND MEASUREMENTS IN VARIOUS TYPES OF HYPERTROPHIC CARDIOMYOPATHY

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Ultrasound measurements were carried out in 45 patients (pts) with hypertrophic cardiomyopathy (HCM). Sixteen had resting outflow tract obstruction (ROTO) and systolic anterior movement (SAM) of the anterior mitral leaflet; 17 had latent OTO (LOTO), OTO only developed with provocation and there was variable SAM; 12 had no OTO (NOTO) at rest or with provocation and there was absent or trivial SAM. Mean septal (S) and posterior (P) wall thickness, S/P ratio, volumes at end-diastole (EDV) and end-systole (ESV), ejection fraction (EF), E-F slope and obstructive indices (OI) were measured and compared to 15 normal subjects.

	ROTO	LOTO	NOTO	NORMALS
S (mm)	26±1.1	21±1.1	17±0.9	10±0.2
P (mm)	14±0.4	10±0.4	10±0.4	9±0.2
S/P	1.9	2.0	1.8	1.1
EDV (cc)	69±8	85±6	84±6	124±8
ESV (cc)	15±2.6	13±1.4	16±2.1	30±2
EF (%)	82±1.4	85±1.6	82±2.3	76±1.1
E-F (mm/sec)	19±3.9	33±4.6	60±4.4	91±5.1
OI	52±5.4	18±5.2	3±1.9	-

HCM is characterized by a disproportionate increase in S and a high S/P ratio. Volumes are reduced and the EF is increased. Compliance is decreased as indicated by a reduced E-F slope. P is only increased in pts with ROTO suggesting that this is a secondary phenomena. In the latter pts S is thickest and these pts have the most reduced EDV's and E-F slopes. These findings indicate that HCM is a continuous spectrum and that pts with ROTO have the severest form of the disease.

FAVORABLE EFFECTS OF NITROGLYCERIN ON ABNORMAL WALL MOTION AND HEART SIZE AT REST AND DURING SUBMAXIMAL ISOMETRIC HANDGRIP EXERCISE IN PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

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We performed serial measurements of left ventricular wall motion (WM) [videotracking] and the radiographic left heart dimension at rest and during submaximal isometric handgrip exercise (HE) (15 to 30% of maximum voluntary contraction) before and after sublingual nitroglycerin (NTG) in 8 patients (pts) with previous myocardial infarction. Mean resting heart rate increased from 68.4 to 75.6 beats/min and systolic BP fell from 142.4 to 133.9 mmHg after NTG (both, $p < .01$). The heart rate-systolic BP product at rest and during HE did not differ before and after NTG. However, the resting left heart dimension decreased from 50.9 to 49.5 mm/m^2 after NTG ($p < .01$). In 4 of 7 pts with abnormal WM at rest, WM improved with NTG and in 3 of these pts complete reversal of abnormal WM occurred. During HE alone the extent of shortening of normal segments increased from 2.8 to 3.6 mm and the peak velocity from 20 to 29 mm/sec in the control state (both, $p < .02$); similar changes during HE occurred in normal segments after NTG. In all 8 pts abnormal WM was exaggerated or induced de novo by HE alone. By contrast, in all 8 pts abnormal WM was improved during HE after NTG, and there was no inducible abnormal WM during HE in 2 pts. We conclude that NTG exerts a favorable effect on myocardial oxygen demand in pts with previous myocardial infarction by decreasing left ventricular chamber size and by improving or reversing resting and exercise-induced abnormalities in left ventricular wall motion.

EFFECTS OF DISOPYRAMIDE PHOSPHATE (NORPACE) ON ELECTROPHYSIOLOGIC PROPERTIES OF ISOLATED CANINE CARDIAC PURKINJE FIBERS

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Disopyramide phosphate (DP) has been reported to suppress ventricular arrhythmias in intact animals. We studied the effects of DP on electrophysiologic characteristics of canine Purkinje fibers (PF) using standard microelectrode techniques. DP,10^{-7}M, had no effect on resting membrane potential (RMP), action potential (AP) amplitude, maximum rate of rise of phase 0 ($\dot{V}_{max}$), and conduction time (CT). At DP,10^{-6}M, AP amplitude and $\dot{V}_{max}$ were decreased, CT was increased, membrane responsiveness was depressed and AP duration and the effective refractory period (ERP) were prolonged. These changes were more pronounced at DP,10^{-5}M. At DP, 10^{-4}M, a marked though reversible decrease in RMP was observed as well. In PF with stable automatic rhythms, DP, 10^{-6}M, decreased the slope of phase 4 depolarization and the spontaneous rate. We studied the effects of changing perfusate{K^+}on the electrophysiologic changes induced by DP,10^{-5}M. At{K^+}= 2mM, the changes in AP characteristics occurred more slowly and were less prominent than at {K^+}= 6mM. In 6 experiments, we perfused PF with Tyrode solution in which sodium was replaced by tetraethylammonium. The AP's in this solution have been shown to be calcium-dependent and have been implicated as a possible mechanism for reentry. In these experiments, DP,10^{-5}M, had no significant effect on the calcium-dependent AP. Thus, the effects of DP are similar to those induced by quinidine-like antiarrhythmic agents. These effects, which are potentiated by higher{K^+}, include depression of the rapid inward current responsible for phase 0 depolarization and prolongation of refractoriness.

THE SIGNIFICANCE OF EARLY CHANGES IN POSITIVE AND NEGATIVE dp/dt FOLLOWING CONTRAST VENTRICULOGRAPHY.

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Contrast ventriculography elicits a complex hemodynamic response. The present study compares dP/dt, both peak positive (P_1) and peak negative (P_2) in the normal (NLV) and abnormal left ventricle (ALV). In 23 patients, heart rate, LVEDP, P_1 and P_2 were measured before and at 30 sec. intervals for 3 minutes after power injection of 40 ml. contrast (Renografin 76) into the left ventricle.

Nine patients had no coronary artery disease (CAD), and normal LV (i.e. normal EDV, ejection fraction and LVEDP). P_1 increased in all maximally at 30 sec. (mean + 48.5% range + 20 to + 160%). Conversely in 14 patients with ALV, P_1 decreased at 30 sec. (mean -17.9% range +8.3 to - 53%).

Though P_2, an estimate of ventricular relaxation, was decreased maximally at 30 sec. in both groups, the reduction was significantly greater with ALV (-32.5% vs -13.2% $p<0.01$). Heart rate was greatest in both groups at 30 sec. and peak LVEDP (between 2-3 min) was the same (16.5 mmHg).

We next examined 11 patients with CAD but NLV. In 9/11 the response was abnormal i.e. there was an abrupt decrease in P_1 and P_2 at 30 sec.

The data indicate that 1) at 30 sec. after ventriculography P_1 will rise in the NLV. 2) Failure of P_1 to increase indicates either ALV or critical obstruction to coronary flow. 3) P_2 decreased in both NLV and ALV suggesting contrast material may alter ventricular relaxation even in the NLV.

IMPAIRED PERIPHERAL VASOCONSTRICTION IN PATIENTS WITH AORTIC STENOSIS: A POSSIBLE MECHANISM OF SYNCOPE.

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Inability to increase peripheral vascular resistance (PVR) in response to a decreased cardiac output (CO) has been suggested as a possible cause of syncope in aortic stenosis (AS). We investigated this relationship by comparing the PVR in nine patients with AS (mean gradient 86 mm Hg) seven of whom had syncope, seven patients with aortic insufficiency (AI) and ten controls (C) during atrial and ventricular pacing (AP and VP) to similar heart rates. None developed syncope or chest pain during the study. The resting (R) heart rates (HR) and CO were similar in the three groups. AP caused no change in the parameters measured. VP produced a significant decrease in CO and increase in PVR with no change in mean aortic pressure (AO) in the C and AI groups. In the AS group, a similar VP-induced decrease in CO was associated with a significant fall in AO pressure but no change in PVR. These data support the concept that failure to vasoconstrict in response to acute decreases in CO may result in hypotension and contribute to syncope in AS.

		HR	AO	CO	PVR
C	R	77±12	104±10	5.1±.8	20±4
	VP	134±9	105±9	4.1±.8*	26±5*
AI	R	86±10	95±20	5.5±.7	17±2
	VP	136±6	98±22	4.4±.7*	23±4*
AS	R	84±9	90±10	5.6±.9	16±3
	VP	129±13	76±10*	4.6±1.0*	17±4

*$p<0.05$

EFFECT OF NITROGLYCERIN ON VENTRICULAR FIBRILLATION THRESHOLD IN THE NON-ISCHEMIC MYOCARDIUM.

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Ventricular fibrillation threshold (VFT) was measured before and after intravenous infusion of nitroglycerin (TNG) in five non-ischemic open chest mongrel dogs anesthetized with sodium pentobarbital. Heart rate was kept constant by crushing the sinus node and pacing from the atria at a cycle length of 400 msec. A stepwise increase in current was delivered after every 15 beats through a bipolar platinum electrode sutured to the left ventricular epicardium. Each current pulse was 2 msec. in width and the duration of the pulse train was 200 msec. The train was delivered 50 msec. after the onset of the QRS complex and had a constant current source. TNG was infused until a steady-state decline in systolic arterial pressure of 15-20 mm Hg was achieved (average 17.5 ug/min for 10 minutes) and maintained at a constant infusion rate thereafter.

	Mean Aortic Pressure	VFT
Control	96 ± 5 mm Hg	28 ± 2 MA
TNG	76 ± 3 mm Hg	51 ± 5 MA
p	<0.01	<0.01

When systolic arterial pressure was returned to control levels by the added infusion of phenylephrine, there was no significant change in VFT when compared to that seen with TNG infusion alone (51 ± 5 vs. 54 ± 7 MA). These results demonstrate that TNG raises the threshold of ventricular fibrillation in the non-ischemic myocardium. This beneficial electrophysiologic effect of TNG is found in the absence of ischemia, and is independent of afterload reduction.

ACUTE HYPOXIC HEART FAILURE: COMPARISON OF HYPOXEMIA AND ISCHEMIA.

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Early ischemic cardiac failure may be due to lack of flow per se,(with a resultant decrease in substrate delivery and metabolite wash-out), lack of O_2 delivery, or both. Accordingly, acute cardiac failure was studied in an isolated working buffer perfused rat heart. Control aerobic developed pressure (DP) with coronary flow (CF)= 12ml/min, pO_2=600mmHg, was 76±2mmHg (n=34). Ischemia (I), with reduction of CF to zero, or hypoxemia (H), induced by rapidly switching to an anaerobic perfusate with CF= 12ml/min,both caused a prompt decrease in DP. The early rapid decrease of DP (as % of control DP/sec) was greater for I than H (4.5±.3 vs. 2.5±.4 % of control/sec ($p<.01$, n=6). After 3 min, DP had fallen to 2±.2 vs. 25±1mmHg ($p<.01$) in the I and H groups, respectively. After 3 min of H or I, reoxygenation (Reoxy) for 20 min resulted in complete recovery of DP. However both H and I demonstrated impaired ventricular relaxation (VR) in the early Reoxy phase with an increase in VR time from a control of 85±3msec to 113±4msec ($p<.01$) after H, and to 123±3 msec ($p<.01$) after I. Control aerobic myocardial lactate extraction was 10% of the 1.0mM perfusate level. Effluent lactate levels were higher with I than with H (2.6±1 vs. 1.8±1mM, $p<.01$, n= 6). But total lactate production in the 3 min hypoxic period was 20±1 vs. 33±1 m mole/mg wet wt ($p<.01$) for I and H respectively.

Thus 3 min of I resulted in higher effluent lactate levels, but less total glycolytic flux, and a more rapid fall of DP than 3 min of H.

Hence, anaerobic flow improved early hypoxic heart performance and metabolism by washing-out lactate, thereby decreasing myocardial acidosis. These metabolic changes did not affect the impairment of VR with Reoxy.

MECHANISMS OF ELECTRICAL ALTERNANS IN LEFT AND IN RIGHT BUNDLE BRANCH BLOCK (BBB): EARLY OR LATE PHASES OF REFRACTORINESS IN THE BUNDLE BRANCH SYSTEM.

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Initiation and perpetuation of alternation of shape and duration of QRS was studied in ECGs of 8 patients. In five, the alternation started only after long cycles. In one of these five the first QRS abnormality was seen in the second beat after the pause (Type I). Thus, the BBB occurred early in the refractory period (RP) (Phase 3 BBB). In the other four the alternating BBB started with the first beat that terminated the pause (Type II) and was attributable to phase 4 (diastolic depolarization) in some "vulnerable" area of the bundle branch system. In Type II, perpetuation of alternation can be explained by shortening of the bundle branch cycle after concealed transseptal conduction of alternate impulses. Thus, phase 3 and phase 4 alternans can be distinguished simply by the configuration of the first beat after a long pause (e.g., in sinus arrhythmia or after a premature beat) and can be confirmed by demonstration elsewhere in long records of isolated BBB patterns with transient shortening of R-R in Type I and prolongation of R-R in Type II. In two of the remaining three patients late (phase 4) QRS-T alternans occurred, in one,in the presence of atrial fibrillation, and in the other, during ventricular pacing. In the third, slowing of heart rate converted alternating BBB to BBB persisting in every beat, but further slowing resulted in persistently normal QRS complexes. This "pseudo phase 4 alternans" can be explained by the absence of concealed retrograde transseptal conduction during alternation but its occurrence during persistent BBB at a slower rate. Thus, the mechanism of QRS alternans is explicable by phase 3, phase 4 or pseudo phase 4 BBB.

THE CARBOXYLIC IONOPHORES - A NEW GROUP OF INOTROPIC AGENTS

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Our previous discovery of the inotropic effects of X-537A has been extended to other carboxylic ionophores (I) including monensin, dianemycin, nigericin, X-206 and A-204. Their cardiovascular effects were studied in anesthetized normal and infarcted dogs. Increases of up to 300% in dP/dt, dP/dt/P and force of isometric contraction were obtained consistently. Cardiac output and aortic pressure increased while total peripheral resistance dropped. Primary and secondary reduction of coronary resistance permitted increases in coronary flow 3-8 fold, LVO_2 consumption increased; and the LV mechanical efficiency improved due to the much greater external LV volume work performed. ^{131}Xe clearance indicated increased nutrient flow in the ischemic region of the infarcted myocardium. Most I produced positive chronotropic effects and, at higher doses, PVC's occurred. AV node conduction was facilitated as determined from the A-H intervals of the His bundle electrogram at progressively increasing paced atrial rates. Studies with α and β blockers showed varying degrees of α and β component effects of I due to probable catecholamine release. The onset of action of I is rapid with maximal response attained in 5-15 minutes, lasting for 2-4 hours and reverting to control values in the next hour. Other systemic effects include elevation of glucagon plasma levels with subsequent glucose and insulin increases, and elevation of Hgb and Hct. The salutary response pattern observed with I justifies considering the I as a new class of inotropic agents with therapeutic potentials of extensive cardiovascular applicability. Furthermore, I provide new tools for probing factors of myocardial contractility, and gaining insight into the mechanism of membrane bound carriers and receptors.

EVALUATION OF THE NON-VALVULAR FACTORS OF CARDIAC PERFORMANCE, LEFT VENTRICULAR CONTRACTILE PATTERN AND CORONARY ANATOMY IN THE MITRAL VALVE PROLAPSE SYNDROME. Anthony N. DeMaria, MD; Hugo Bogren, MD; Christopher C. Caudill, MD; Louis A. Vismara, MD; Richard R. Miller, MD; Ezra A. Amsterdam, MD, FACC; Alexander Neumann, BS; Dean T. Mason, MD, FACC. Univ. of Calif., Davis, Calif.

Controversy exists regarding the relation of the mitral valve prolapse syndrome (MVP) to coronary anatomy, left ventricular (LV) dyssynergy and cardiac performance. Thus, coronary arteriography (CA), LV cineangiography (cine) right and left heart pressures and cardiac index were analyzed in 25 MVP patients. Pulmonary artery wedge pressure was elevated in only 2 patients and the mean value for the group was 9 mmHg. LV end-diastolic pressure was elevated to greater than 12 mmHg in 4 patients (mean 15 mmHg) and the mean value for the group was 10 mmHg. Cardiac index for the group was 3.7 L/min/M^2 and was abnormal (depressed to less than 2.5 L/min/M^2) in only 2 patients. CA revealed luminal stenosis of greater than 75% in only 2 MVP patients and the distal posterior left circumflex artery, which was absent in 10/26 (38%) controls, was absent in an equivalent number of MVP patients, 7/21 (33%). LV cine revealed a normal contractile pattern in 18/25 (72%) while ventricular dyssynergy was found in 6 patients (20%) with normal CA and was confined to the region of the stenotic vessel in 2 patients (8%) with abnormal CA. Thus, MVP is associated with normal CA and LV performance in nearly all patients. Dyssnergy on LV cine occurs in a minority of MVP patients and may occur in the absence of coronary disease. These data indicate that the etiology of the MVP syndrome primarily involves pathology of the mitral valve apparatus rather than the coronary arteries or ventricular myocardium.

SHORT TERM PROSPECTIVE FOLLOW-UP OF PATIENTS WITH CHRONIC RIGHT BUNDLE BRANCH BLOCK AND LEFT POSTERIOR HEMIBLOCK Ramesh Dhingra, MD; Ruben Chuquimia, MD; Delon Wu, MD; Ali Ehsani, MD; Pablo Denes, MD; Kenneth M. Rosen, MD, FACC, University of Illinois, Chicago, Illinois.

It has been suggested that right bundle branch block (RBBB) with left posterior hemiblock (LPH) is associated with high risk of trifascicular heart block. This hypothesis was examined in 21 patients (pts) with chronic RBBB, axis of +100° to +180°, and absence of right ventricular hypertrophy. The group consisted of 19 males and 2 females with mean ± SEM age of 61 ± 2. Initial studies revealed A-H intervals of 58 to 152 msec (mean 103 ± 6) and H-V of 40-80 msec (mean 52 ± 2). Six pts (28%) had prolonged H-V (>55 msec). All pts were prospectively followed in a research clinic (mean follow-up of 487 ± 62 days). Three of 21 pts (16%) needed permanent pacemakers for development of the following symptomatic conduction disease: sino-atrial block (day 3), site undetermined 2° A-V block (day 118), and 2° block proximal to H (day 398). Two pts died of non-cardiac disease, and one died suddenly (day 571).

In conclusion, RBBB with LPH was associated with less trifascicular disease than expected. Symptomatic conduction disease occurred, but could only be possibly related to trifascicular disease in two of the pts. This short-term data suggests that prophylactic demand pacing is not indicated in patients with chronic RBBB and LPH.

(see Addendum)

DIGITALIS INDUCED ALTERATION OF CORONARY REACTIVE HYPEREMIA: A POTENTIAL DELETERIOUS EFFECT
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In the presence of myocardial ischemia, altered responsiveness to digitalis glycosides has been implied. To clarify this clinical assumption, the effects of increasing doses of Acetylstrophanthidin (AS) were examined in 6 dogs with chronically implanted coronary artery and aortic flow probes and a balloon occluder on the left circumflex coronary artery. Left ventricular (LV) and aortic pressure, LV dp/dt and coronary and aortic blood flows (CBF and ABF) were measured before and after cumulative digitalizing doses of 0.025 mg/kg. AS until ventricular tachycardia. Heart rate was controlled with atrial pacing. During each of these periods coronary flow responses to 10 second occlusions were also recorded. In the control state reactive hyperemia index (RHI), that is CBF post/CBF pre occlusion averaged 3.37 ± 1.1 ($P < 0.01$). AS increased LV dp/dt by 31% ($P < 0.01$) and systemic vascular resistance by 10% ($P < 0.01$) while ABF did not change and CBF decreased by 30% ($P < 0.01$) and coronary vascular resistance increased by 40% ($P < 0.05$). RHI decreased successively with cumulative doses of AS averaging 142% less post AS dose #2 ($P < 0.05$). Peak RHI during the control period occured 2.5 seconds after occlusion ceased but post AS peak RH was delayed to an average of 14 seconds post occlusion. This altered coronary vasomotor reactivity may relate to the clinically observed phenomenon of digitalis sensitivity in patients with ischemic heart disease.

QUANTITATIVE ASSESSMENT OF LEFT VENTRICULAR FUNCTION FOLLOWING SUCCESSFUL MITRAL VALVE SURGERY
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Several indices of left ventricular (LV) function were analyzed in 19 patients an average of 11 months following mitral valve surgery for stenosis (MS), chronic regurgitation (MR), or combined lesions (MS-MR) in those with good postoperative valve function. Biplane LV angiography with high quality LV pressure recordings was used to construct LV pressure-volume diagrams with computer techniques. The 2 combined groups with MS and MS-MR showed a significant decrease in A-VO_2 difference ($p < .025$), MR, and mitral valve gradient ($p < .05$). There were no significant changes in LV end-diastolic pressure (LVEDP), LV mass (LVM), volumes, ejection fraction (EF), mean velocity of circumferential fiber shortening (VCF), LV work or power. Patients with MR showed an increase in systolic blood pressure (SBP) ($p < .025$) and decrease in LVEDP ($p < .05$), MR ($p < .025$), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV systolic work ($p < .01$). The EF fell from 55±13% to 43±16% ($p < .05$) and mean VCF fell from .51±.09 to .36±.01 ($p < .05$). LVM failed to regress following surgery (preop 142±56, postop 144±58g/M^2). These findings indicate that surgical correction of MS, or MS-MR, is not associated with significant changes in LV geometry or function. Correction of chronic MR results in improvement in LVEDP and LVEDV (reduction in preload). This reduction, combined with elevation in afterload (elevated SBP) and loss of low impedance outflow (MR), results in reduced EF and VCF postop. These changes were not associated with regression in myocardial hypertrophy. Successful correction of chronic mitral valve dysfunction fails to improve LV performance and does not result in reduction in LVH.

LATE CARDIAC TAMPONADE AFTER OPEN HEART SURGERY: A PROBLEM OF DIFFERENTIAL DIAGNOSIS.

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Cardiac tamponade may be a life threatening complication of otherwise successful cardiac surgery. Nineteen cases of post-operative tamponade have been recognized at our institution. Fourteen of these occurred in the late post-operative period (LCT) between days 6 and 31. Surgical procedures were valve replacement (8), mitral commissurotomy (1), and coronary bypass (5). All patients had median sternotomy with the pericardium left widely open. In 3 patients LCT was temporally related to epicardial pacemaker wire removal and in two to complications of severe paroxysmal hypertension. Coumadin anticoagulation had been used in 7 of 14 and in 3 the prothrombin time was excessively long. Symptoms included pain in the chest (4), abdomen (2), and back (3), dyspnea (6), and nausea (3). High venous pressure and signs of impaired peripheral perfusion were present in all patients with LCT. Other helpful signs were widening mediastium (7), drop in hematocrit (4), pulses paradoxus > 12 mm Hg (9), and echocardiographic evidence of enlarging effusion (1). Therapy consisted of prompt removal of mediastinal fluid by needle aspiration alone (8), needle aspiration followed by thoracotomy (2), immediate thoracotomy (1), or bedside subxyphoid exploration (3), followed by steroid therapy. Evacuation of fluid was effective in releaving LCT however recurrent LCT occurred in 3 patients and one of these died with retro-grade aortic dissection from the site of vein graft anastomosis. LCT after cardiac surgery is not uncommon and requires a high index of suspicion for proper diagnosis and management.

ABNORMAL MYOCARDIAL LACTATE METABOLISM AS AN ADDITIONAL FEATURE OF THE SYNDROME OF MITRAL VALVE PROLAPSE

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The syndrome of mitral valve prolapse (MVP) in the presence of normal coronary arteries often presents with chest pain and ECG abnormalities suggestive of myocardial ischemia. To assess the pathogenetic basis of these findings, myocardial metabolic studies at rest, during atrial pacing and in the immediate post pacing period were performed on 19 patients (6 males, 13 females) with MVP. Nine patients (46.3%) had abnormal myocardial lactate extraction (< 10%) ranging from -26% to +6% with a mean of -1± 10.4. LV dyssynergy was noted in 8 of the 19 (42%) patients, 4 of whom had abnormal lactate metabolism (LM). All patients had normal coronary arteriograms. Three patients had abnormal left ventricular end diastolic pressure and 1 of those had abnormal LM. Nine patients had normal ECG's, lactate metabolism being abnormal in 3. Non-specific ST-T changes were present in 6, 5 of those having abnormal LM. Left axis deviation was present in 2, and LBBB in 1 patient with normal LM. The unusually high incidence of abnormality of myocardial lactate extraction and ventricular dyssynergy suggest that myocardial hypoxia may be an important contributing factor in this syndrome.

EXPERIENCE WITH 3835 PACEMAKERS UTILIZING TRANSTELEPHONIC SURVEILLANCE

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A telephone system providing warning of malfunction must be simple and capable of detecting battery, electrode, or component failure. Transtelephonic monitoring of 3835 pacemakers over 4 years (11,928 patient months) prediced battery failure in 411 of 416 patients. All unpredicted failures occurred in pacemakers with defective rate decay circuitry. The mean time to removal was 24.9 months. Of 275 pacemakers still functioning, 450 are older than 24 months, (mean 30.6 months). Another 96 pacemakers were removed for other malfunctions; lead fracture 6, lead displacement 30, component failure 30, lack of capture 21, lack of sensing 9. 121 of the 512 malfunctions occurred before 18 months, with 67 due to premature battery failure. Serious arrhythmias unrelated to the pacemaker were detected in 325 instances. Transtelephonic monitoring has increased pacer implants from a 2 year elective removal time to beyond 30 months. It has proved to be a simple, reliable technic to identify pacer malfunction and serious arrhythmias. Unexpected early failure or malfunction is significant. Hence, a precise surveillance program appears mandatory to detect unexpected pacemaker malfunction.

CLINICO-PATHOLOGICAL FINDINGS AND SURGERY IN INFRADIAPHRAGMATIC TOTAL ANOMALOUS PULMONARY VENOUS RETURN

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Twenty seven cases of infradiaphragmatic total anomalous pulmonary venous return (ITAPVR) seen at Texas Children's Hospital between 1957 and 1974 were divided into two groups; A (uncomplicated) 16 in which 14 patients had a ductus arteriosus in addition, and B (complicated) 11 patients with associated major intracradiac defects; 6 with asplenia. Clinically Group A patients (ages 1 day to 7 ½ weeks) all presented with varying degrees of tachypnea and cyanosis. Physical findings were not specific. Mean delay from onset of symptoms to surgery or death was 15 days. At cardiac catheterization, ITAPVR was diagnosed in 11/13. Angiography was essential for demonstrating site of anomalous drainage, while oxygen saturations were not helpful. Pulmonary hypertension was present in all. Suprasystemic in 7/10. In 5 patients (2 of whom had cardiac catheterization) the diagnosis of TAPVR was not made prior to death. Eight patients had corrective surgery with 50% survival. One late death at 3 months was due to stenosis of the surgical anastomosis. Long term survival was 37%. The poor prognosis in ITAPVR was related to the degree of obstruction, high pulmonary vascular resistance, delay in diagnosis and anatomically small left heart.

A QUANTITATIVE ANALYSIS OF THE HETEROGENEITY OF BLOOD FLOW TO SMALL ADJACENT SEGMENTS OF THE LEFT VENTRICLE.

James Ehrhardt, Ph.D.; Melvin L. Marcus, M.D.; Richard E. Kerber, M.D., FACC; and Francois M. Abboud, M.D., FACC, University of Iowa, Iowa City, Iowa.

Although coronary flow to large areas of the left ventricle is nearly evenly distributed, there is considerable heterogeneity of flow to small adjacent segments (SAS) of the left ventricle. In 25 open chest dogs we studied the heterogeneity of blood flow to SAS of the left ventricle (32 endocardial, 32 mid-wall, and 32 epicardial segments per dog; ave. wt. = 0.78 ± .04 gms.) Labelled 9μ microspheres were utilized to determine the segmental flows. In each study, the standard deviation (SD) of the perfusions of all 96 segments was determined. These standard deviations were normalized for all 25 studies (SD x 100 ÷ the $\bar{X}$ flow for each dog.) The average normalized standard deviation was 17.9 ± 2.0%. Thus, on the average, in dogs with an unimpaired coronary circulation, segmental flows of less than 54% of mean flow occur infrequently (-2 SD = 2.3%) and segmental flows less than 46% of mean flow occur rarely (-3 SD = 0.1%). There was more heterogeneity of flow to the SAS in the epicardial layer than to the SAS in the mid-wall or endocardial layers (normalized SD of 19.2 ± 1.1% vs. 13.2 ± 0.8% and 15.5 ± 0.9% respectively [$p < 0.05$]). The variability inherent in the microsphere technique was independently assessed (injection of multiple batches of labelled microspheres simultaneously) and found to be 3 ± 2%. Conclusion: In all layers of the myocardium (particularly the epicardium) considerable heterogeneity of flow to SAS can be demonstrated, even when technical sources of variation are accounted for. This heterogeneity of flow to SAS of the left ventricle may be due to transient spontaneous changes in the microcirculation.

INEFFECTIVENESS OF PRACTOLOL A CARDIOSELECTIVE BETA BLOCKER FOR THE TREATMENT OF ANGINA PECTORIS.

Ghanem Elias MD. FACC; Jacques Le Lorier MD.PhD. Maisonneuve and Hotel-Dieu Hospital,Department of Medicine and Pharmacology, University of Montreal. A clinical trial of 7 month's duration was carried out on 18 patients having at least 5 anginal attacks per week. The study was divided into 2 periods(A and B). A single blind Dose-Finding period (A) lasted 10 weeks on placebo(Pl), and 2 weeks on 400,800,1200mg of Practolol (Pr) Q.I.D. respectively. Physician evaluation based on anginal episodes counts, Nitroglycerin consumption(N) and exercise stress testing at the end of each dose period were used to select the optimal dose for each patient. Optimal treatment was 400mg Q.I.D. for 2 patients and 1,200mg Q.I.D. for the remaining 16. Subsequently and after a 2 weeks washout period the optimal dose of Pr was tested against Pl (Period B) using a double blind double crossover Design divided into 4 periods lasting 4 weeks each. The patients received Pr during two of these periods and Pl during the other 2. No significant Difference between Pr and Pl was seen in the frequency of Anginal episodes, N consumption, blood pressure and exercise stress testing. A significant difference ($P < 0.01$) was noted in the heart rate at rest and at the end of the exercise test. Thus although the doses used produced Beta Blockade, they did not lead to objectively demonstrable therapeutic effect.

ELECTRODE CATHETER RECORDINGS DURING MALIGNANT VENTRICULAR ARRHYTHMIAS FOLLOWING EXPERIMENTAL ACUTE MYOCARDIAL ISCHEMIA. EVIDENCE FOR RE-ENTRY DUE TO CONDUCTION DELAY AND BLOCK IN ISCHEMIC MYOCARDIUM.

Nabil El-Sherif, MD; Benjamin J. Scherlag, PhD; Ralph Lazzara, MD, Veterans Administration Hospital and Univ. of Miami School of Medicine, Miami, Florida.

In fifteen anesthetized open-chest dogs, plunge wire and electrode catheter recordings of the His bundle electrogram containing septal activation were monitored before and after ligation of the anterior septal artery. The average time of onset of ventricular tachycardia was 5 minutes. The evolution of the arrhythmia was temporally related to progressive fragmentation and delay of the septal potential resulting in a marked increase in total ventricular activation time (up to 335 msec). In six experiments the fragmented, delayed septal depolarization was inscribed well beyond the T wave of the surface QRS prior to the onset of the arrhythmia. Various conduction disorders involving the ischemic septal myocardium were observed which closely correlated to the patterns of coduction disorder in the ischemic proximal His-Purkinje system. First degree block, 2° block of the Mobitz II and Wenckebach types, higher degree block and paroxysmal complete block were demonstrated. The onset of the arrhythmia was characteristically associated with a Wenckebach pattern of conduction delay of a part of the septal deflection. Conduction disorders of the ischemic myocardium were tachycardia-dependent. In summary, the study shows that the basic prerequisites for re-entry do exist during the early period following occlusion of a major coronary artery and can explain the malignant phase of ventricular arrhythmia. The described changes in the electrode catheter recordings are of particular interest for they raise the possibility that similar disorders in man may be detected by the same procedure.

MAXIMAL INSTANTANEOUS MITRAL VALVE VELOCITIES MEASURED WITH A DIGITAL ECHOCARDIOGRAPHIC TRACKING SYSTEM

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Analysis of the motion of various cardiac structures is attaining increasing clinical significance. By coupling a digital tracking system to a commercially available echocardiograph, we have been able to obtain continuous position and velocity data from selected intracardiac structures. This tracking system, which employs a dynamic range gate, has been designed to isolate and lock on to a selected target within the heart. Position of the target is calculated every 8 milliseconds; velocity is obtained by determining the difference between consecutive positions. This system has been used to study mitral valve motion in 20 normal subjects. Maximal instantaneous velocities of the anterior leaflet of the mitral valve during early diastolic opening (D-E), mid-diastolic closure (E-F), atrial systolic opening (F-A), and end diastolic closure (A-C) were recorded. The following results were obtained.

Segment of Mitral Cycle	Maximal Instantaneous Velocity (mm/sec) Mean	Range	Standard Deviation
D-E	430	331 to 651	83
E-F	362	236 to 472	64
F-A	236	131 to 398	79
A-C	346	230 to 467	78

These instantaneous velocities are to be distinguished from the average velocities obtained by manually measuring the slopes of the curve segments. This system demonstrates a new technique for obtaining more detailed information about the dynamic characteristics of selected cardiac structures.

FUNCTIONAL APPRAISAL OF SINUS NODE ARTERY DISEASE

Toby R. Engel, MD; Steven G. Meister, MD; Gilson S. Feitosa, MD; Herbert A. Fischer, MD; William S. Frankl, MD, FACC, The Medical College of Pennsylvania, Philadelphia, Penna.

The relationship of depressed sinus node function to coronary artery disease (CAD) remains uncertain. The sinus node artery (SNA) was easily identified in all of 80 unselected normal coronary arteriograms. Angiographic disease of, or significant obstruction proximal to the SNA was seen in 21% of 80 unselected CAD patients. Heart rate and sinoatrial recovery times (SART) were obtained in 50 consecutive unmedicated patients prior to arteriography. There was no difference ($p > 0.25$) between the SART of 23 CAD patients free of SNA involvement (1092 msec $\pm$55 SEM) and 18 normals (1070 msec $\pm$ 40 SEM). Nine patients with SNA involvement had shorter SART (941 msec $\pm$ 52 SEM) than normals ($p < 0.05$) or other CAD patients ($p > 0.05$). Similar results were obtained for heart rate. No patient with SNA involvement had a prolonged SART or sick sinus syndrome (SSS). Six of the 50 patients studied were symptomatic with SSS. Five of these SSS patients had CAD but none had angiographic evidence of SNA involvement. Obstructions involving the SNA were commonly present in CAD but were not associated with altered heart rate or SART. Patients with SSS exhibited no angiographic evidence of SNA involvement. Therefore it is unlikely that SSS is related to CAD of the SNA.

HEMODYNAMIC RESULTS FOLLOWING COMPLETE ATRIO-VENTRICULAR CANAL DEFECT REPAIR

E. Esplugas, MD; L. Kidd MD, FACC; P.M. Olley MD, FACC; G.A. Trusler MD.

Over the past 5 years we have repaired complete atrioventricular canal defects with a technique which includes VSD closure with a large patch on its LV aspect, complete repair of the mitral valve cleft, and patch repair of the ASD. Eight patients repaired by this technique (age at operation 2½ months-10 yrs) were catheterised 6-31 months post-op (PO). All 8 were asymptomatic when studied. Three had also been debanded and in 4 separate secundum ASD was sutured. Three were hemodynamically normal and 1 had a small residual shunt (Qp/Qs 1.4/1) A fifth patient had a large atrial and ventricular shunt (Qp/Qs 2.4/1) with elevated pulmonary vascular resistence and moderate mitral regurgitation. All 8 patients had normal LV ejection fractions (59-72%) but six had LV end diastolic volumes $>$ 84 mls/M^2 Three patients had areas of LV dyskinesis associated with ECG and VCG evidence of myocardial necrosis in two and increasing LV voltages PO in the third. All three had temporary PO heart failure In only one patient was a mitral valve gradient found.

All patients remained in normal sinus rhythm with left axis deviation; transient heart block occurred PO in 1 this being the only patient to develop complete right bundle branch block. Type B WPW present pre-op in one patient disappeared following surgery. His bundle electrograms could only be recorded in three patients, HV intervals were normal and AH prolonged in only one.

While the immediate hemodynamic results indicate a good surgical repair in 7/8 patients studied; there is evidence to suggest that some of these children may have further problems due to impaired myocardial performance.

THE INFLUENCE OF DIABETES AND HYPERTENSION ON THE RESULTS OF CORONARY REVASCULARIZATION

Richard M. Engelman, M.D., FACC, J. Ganesh Bhat, M.D., Ephraim Glassman, M.D., Frank C. Spencer, M.D., Arthur D. Boyd, M.D., Boris S. Pasternak, Ph.D., George E. Reed, M.D., and O. Wayne Isom, M.D. New York University Medical Center, New York, NY

The effects of diabetes (D) and hypertension (H) on the early postop course of patients undergoing coronary revascularization were studied by reviewing the records of 177 patients operated upon in 1972. Multiple bypass grafts were performed in 30/32 H (94%), 8/10 D (80%), 12/14 DH (85%), and 102/121 NDH (neither diabetic nor hypertensive) (84%). The cumulative incidence of postop low cardiac output, renal failure and arrhythmia was highest in the H and DH groups (P .05). Operative mortality was 0 in D, 2.5% in NDH, 9.4% in H and 14.3% in DH. The late results of coronary revascularization were analyzed in 103 patients in whom both pre and postop catheterizations were performed. Mean elapsed time between op and postop cath was 9.4 months. There was no significant difference in the progression of atherosclerosis in the ungrafted coronary arteries between the NDH group (11%), D group (6%), H group (16%), and DH group (20%). Similarly, graft occlusion was not significantly affected by D or H averaging 26% (NDH), 15% (D), 16% (H), and 33% (DH). This study has shown that while H contributes to increased morbidity and mortality in the immediate postop period, neither D nor H appear to influence the subsequent results of coronary revascularization.

ORIGIN OF VENTRICULAR ARRHYTHMIAS CAUSED BY DIGITALIS

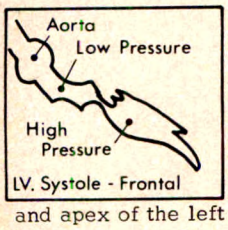
Philip O. Ettinger, MD, FACC; Timothy J. Regan, MD, FACC; Henry A. Oldewurtel, New Jersey Medical School, Newark, New Jersey.

Digitalis-induced ventricular arrhythmias might originate in Purkinje tissue or ventricular muscle. To examine this, acetylstrophanthidin (AS, 25 µg/min) was perfused into a limited zone of myocardium in 16 intact anesthetized dogs thru a catheter fluoroscopically placed in the left anterior descending artery. A second catheter in the great cardiac vein sampled venous effluent from this region and monitored coronary flow (^{85}Kr). We monitored His (H), left bundle branch (LBB) and intramural electrograms from endocardial and epicardial sites. No conduction alterations preceded the onset of arrhythmia. After 3-5 minutes of AS, ventricular tachycardia began; great cardiac vein K^+ rose from 3.8$\pm$0.2 to 5.1$\pm$0.3 mEq/L ($P<0.001$), indicating egress from the perfused zone without ischemia. Five animals (Group 1) were sacrificed two minutes after onset of arrhythmia while the remaining 11 (Group 2) continued until ventricular fibrillation (4-11 min.). All initially showed normal (endocardial→epicardial) transmural depolarization, but 9/16 demonstrated reversal, usually late during arrhythmia, including 8/11 in Group 2. Epicardial→endocardial sequences preceded QRS onset and H and LBB activation. Myocardial K^+ was reduced (mean, 63$\pm$2 µEq/g) and Na^+ increased (mean, 43$\pm$2 µEq/g) in the perfused zone (nonperfused circumflex area K^+ 72$\pm$1, Na^+ 34$\pm$2 µEq/g, $P<0.01$ for both); changes were similar in inner and outer ventricular wall and more pronounced in Group 2. Reversal of transmural activation sequence with epicardial depolarization preceding QRS onset during arrhythmia suggests origin within myocardium; electrolyte gradients between adjacent regions may be causative.

A VARIANT OF HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY: MIDVENTRICULAR OBSTRUCTION.

Raul E. Falicov, M.D., FACC; Leon Resnekov, M.D., FACC; Saroja Bharati, M.D.; and Maurice Lev, M.D., FACC, The University of Chicago, Chicago, Illinois.

The site of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy (HOCM) is currently thought to be at the outflow tract between the bulging hypertrophic septum and the anterior leaflet of the mitral valve which impinges on the septum during systole. We have studied three patients where the site of left ventricular obstruction was in the mid-ventricular area, not the outflow tract. This was confirmed by left ventricular angiography in all three patients, simultaneous pressure measurements in the inflow, outflow, and apex of the left ventricle in one patient demonstrating peak systolic gradient of 130 mmHg between the apex and both inflow and outflow tracts (catheter entrapment artifact ruled out by catheter with 12 side holes,, free withdrawal of blood during systole, and angiographic appearance demonstrating contrast medium at end systole where the catheter tip was located) (Figure), and autopsy findings of mid-ventricular septal bulging in one patient who died suddenly six months after myectomy of the left ventricular outflow. Recognition of this variant form of HOCM is essential for choice of surgical approach, since outflow septal myectomy or mitral valve replacement will be ineffective in relieving the intraventricular obstruction in these patients.



COLLATERAL BLOOD FLOW IN THE BORDER ZONE FOLLOWING ACUTE CORONARY OCCLUSION

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Coronary occlusion reduces flow in an area larger than the ultimate infarct. To determine if partial ischemia spares a border zone, myocardial flow was measured with 15μ microspheres in 41 anesthetized open chest dogs following ligation of the left anterior coronary artery (LAD). Tissue supplied by the artery was delineated by dye injection. Intramural stained tissued did not correspond to epicardial landmarks, but by careful dissection the tissue was separated along the stained border. 10 mins after occlusion, flow in the non-ischemic (unstained) tissue adjacent to the border was normal, while the immediately adjacent (stained) tissue was nearly as ischemic as more central samples. 71% of the decrease in flow occurred at the border while only an additional 29% decrease occurred within the ischemic area. Flow supplied by adjacent vessels to normal tissue in the stained samples was determined by microspheres injected while perfusing the LAD with unlabelled blood at aortic pressure. This flow remains following occlusion and was subtracted from measured flow. Thus the flow gradient from ischemic tissue at the border to the center was only 11% of the maximal decrease. A smaller transmural gradient was also present. Results were similar at 2 hours. We conclude tissue supplied by an artery is made nearly as ischemic at the border as in the center following acute occlusion. Measurements of intermediate flows in a border zone may result from mixed normal and ischemic samples. Thus survival of border tissue following coronary occlusion may depend on factors other than the distribution of immediate collateral flow.

INCIDENCE AND REPRODUCIBILITY OF VENTRICULAR ARRHYTHMIAS DURING MAXIMAL EXERCISE TESTING IN NORMAL MEN

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The clinical significance of ventricular premature complexes (VPC) during maximal treadmill exercise tests (MTET) in normals is still uncertain. This study was carried out to document the incidence and reproducibility of VPC during MTET. The study population consisted of 465 subjects free of heart disease who completed 2 serial MTET an average of 3 years apart. On repeat MTET, VPC were observed in 37% of the 25 to 34 year olds, 41% of the 35 to 44 year olds, and 52% of the 45 to 54 year olds. This compared closely to the previously reported incidence during their first MTET of 29%, 34% and 43%, respectively. VPC were typed as simple (rare or occasional) or complex (frequent, multifocal, or consecutive). The incidence of complex VPC was small in each age group and similar in all groups. Individual reproducibility was as follows:

	No.		No.	
VPC Test One	150	Reproducible Test Two	83	(45%)
		Not Reproducible	67	(55%)
VPC Test Two	187	Subjects with New VPC	104	(56%)

In the 83 subjects with VPC on both MTET, 43 (52%) had VPC reproducible both in frequency and type, while the remaining 48% varied in frequency and/or type. We conclude that the overall incidence of VPC in serial MTET in this normal population remained nearly constant, with the increased incidence in test two reflecting improved detection techniques and the advancing age of the subjects. However, an individual's probability of demonstrating VPC on consecutive MTET appeared to be a chance phenomenon.

EARLY POST-INFARCTION AMBULATORY MONITORING AND EXERCISE TESTING IN DETECTION OF ARRHYTHMIAS

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In 15 patients (pts) free of heart failure and unstable angina at 3 to 11 weeks post myocardial infarction (MI) the nature of ventricular ectopic activity (VEA) was studied by Holter ambulatory electrocardiography (H) and by multistage treadmill testing (MSTT). VEA on 10 hr H tapes was quantitated by a semi-automatic computerized system. MSTT at 3 weeks was carried to peak heart rate of 130 or to abnormalities noted at lower rates whereas at 11 weeks MSTT was symptom-limited. VEA was classified as simple (isolated, uniform, 3/min by MSTT and 9/15 min by H) or as complex (frequent, bigeminy, pairs, multiform, R-on-T, ventricular tachycardia).

Analysis of VEA	3 weeks		11 weeks	
	H	MSTT	H	MSTT
any	13	4	14	9
complex	0	1	11	4
	+H - MSTT	-H +MSTT	+H -MSTT	-H +MSTT
any	9	1	5	0
complex	0	1	4	1

Peak PVC/15 min by H was 4.2 vs. 68.3 respectively at 3 and 11 weeks ($p<0.0001$).

There was no significant difference in infarct size as reflected in CPK measurement between pts with and without complex VEA. AT 11 wks 4/4 pts with prior MI had complex VEA by H or MSTT vs. 7/11 with first MI. It is concluded that 1) peak frequency of all VEA and prevalence of complex VEA increases markedly between 3 and 11 weeks following MI, suggesting the value of *serial* H recordings. 2) Yield of any VEA and of complex VEA is greater with H than with MSTT at 3 and 11 weeks post MI.

MECHANISM OF MORPHINE ARTERIOLAR DILATION: CENTRAL ATTENUATION OF CO_2-INDUCED VASOCONSTRICTION. Stephen F. Flaim, John H. Eisele, & Robert Zelis, MD,FACC, Depts. Medicine, Anesthesiology, & Human Physiology; Univ. of Calif. Davis, California and Penn. State Univ. School of Medicine, Hershey, Penna.

Morphine (MS) may relieve pulmonary edema by attenuating the central nervous system (CNS) sympathetic alpha adrenergic transmission resulting in venous pooling from arteriolar dilation. To clarify this mechanism, the effect of MS on the cardiovascular system under CO_2 challenge was determined in 10 normal subjects. Forearm blood flow was measured plethysmographically and forearm vascular resistance (FVR) calculated. CO_2 challenge was rebreathing 7% CO_2, 30% O_2, 63% N_2 for 5 minutes while FVR, $PaCO_2$ and $PACO_2$ were measured. Intravenous MS (15 mg) decreased FVR 58.8 to 34.4 mm Hg/ml/min/100 ml, $p < .01$), increased $PaCO_2$ (40.3 to 43.5 mm Hg, $p<.01$), and $PACO_2$ (5.76 to 6.42%, $p<.01$). With CO_2 challenge pre MS, FVR increased to 75.5 at peak $PaCO_2$, whereas after MS FVR with CO_2 increased to 45.0 ($p<.01$). ($PaCO_2$: pre MS, 55.3; post MS 56.8, $p>.4$. $PACO_2$: pre MS 8.16, post MS 8.25, $p > .5$). Intravenous Naloxone (1.2 mg) alone failed to alter FVR: however, after MS it increased FVR from 40.5 to 54.4 ($p<.02$), and during CO_2 challenge FVR increased normally to 87.0 ($p<.02$). These data suggest that MS induces an arteriolar dilation by attenuating the reflex effects of CO_2 on FVR. The fact that Naloxone, a CNS narcotic antagonist, reversed this attenuation supports the concept that MS effect on vascular resistance is centrally mediated.

PROSTHETIC VALVE REPLACEMENT IN CHILDREN Michael D. Freed, MD, Amnon Rosenthal, MD, William F. Bernhard, MD, Children's Hospital Medical Center, Boston, Massachusetts.

Although prosthetic valve replacement for the treatment of acquired disease in adults has been widely accepted, similar operations in children are infrequent. Since 1964 we have replaced valves in 54 children, the youngest of whom was 9 months. Twenty-eight were in the mitral position (MVR), 21 aortic (AVR), 1 tricuspid (TVR) and 4 double (DVR).

The most common causes for AVR were ventricular septal defect with aortic regurgitation (AR) in 7 patients (pts), and complications of bicuspid aortic valves; aortic stenosis, 6 pts, and AR secondary to bacterial endocarditis (BE), 4 pts. Severe mitral regurgitation associated with endocardial cushion defects necessitated MVR in 10 pts and rheumatic heart disease in 7 pts.

Eleven different types of valves were inserted. Starr Edwards was most commonly used for AVR and Kay-Shiley for MVR.

The operative (14%) and late (14%) mortality for AVR was lower than for MVR (25% and 15% respectively). TVR and DVR were very hazardous with only 1 of 5 survivors. The operative mortality between 1964 and 1966 was 46% (6/13) compared to 17% (7/41) between 1967 and 1974. Operative mortality under 6 years of age was 64% (7/11) compared to 14% (6/43) in older children. Actuarial tables show a projected 10 year survival of 61 $\pm$ 12% for AVR and 58 $\pm$ 10% for MVR. Complications encountered included thromboembolism (6 pts), severe bleeding secondary to anticoagulation (5 pts), and BE (2 pts) and were more common with MVR than AVR. Growth and development has been normal and did not necessitate a second operation. While not a panacea, VR in children may be life saving and has a definite place in carefully selected children.

HEMODYNAMIC AND ANGIOGRAPHIC CORRELATES OF ISCHEMIC HEART DISEASE TO SUBSEQUENT SUDDEN DEATH. James Foerster, MD; Richard R. Miller, MD; Anthony N. DeMaria, MD; Dean T. Mason, MD, FACC; Ezra A. Amsterdam, M.D., FACC; Louis A. Vismara, MD. Univ. Calif. Davis, Calif.

To evaluate hemodynamic-angiographic variables of coronary artery disease(CAD) to subsequently occurring sudden death (SD) 86 patients medically managed were followed an average of 35 months postcatheterization. There were 14 SD, 62 survivors(S) and 11 other deaths. SD was related to extent of stenosis CAD(>75% narrowing): 1 vessel 0 SD, 32S ($p< .05$); 2 vessel 6 SD, 14 S ($p>.05$); and 3 vessel 8 SD, 16 S ($p<.05$). Although stenosis of the left anterior descending artery(LAD) predisposed to SD(12/14 SD, 34/66 S $p<.05$), it was not predictive for SD when the S group was adjusted for the same extent of CAD: 21/14 SD, 26/30 S ($p>.05$). Further, prognosis was not related to segmental abnormalities in anterior left ventricular wall motion, or to the presence of coronary collateral circulation(6/14 SD, 18/30 S; $p>.05$). Variables of cardiac pump function to SD in all patients with 2 or 3 vessel CAD were evaluated:

	BP[1]	LVEDP[2]	CI[3]	SWI[4]	EF[5]	EDI[6]
SD	92*	17.5*	2.49*	33*	.43*	156*
S	91*	14.8*	2.89*	39*	.45*	144*

(1 blood pressure mm Hg; 2 left ventricular end diastolic pressure mm Hg; 3 cardiac index; 4 stroke work index gm-M/sec^2; 5 ejection fraction; 6 end diastolic volume index cc/M^2; * $p>.05$). Thus, SD occurred in the presence of multivessel CAD. Although LAD stenosis was frequent in SD pts, SD could not be predicted by the anatomic site of CAD, segmental LV abnormalities, coronary collaterals, or parameters of cardiac pump function.

ASPIRIN THERAPY IN ANGINA PECTORIS: EFFECTS ON EXERCISE TOLERANCE, PAIN THRESHOLD, AND PLATELET AGGREGABILITY William Frishman, MD; James Christodoulou, MD; Babette Weksler, MD; Charles Smithen, MD; Thomas Killip, MD, FACC, Cornell Medical Center, New York, N.Y.

If altered platelet function contributes to poorly perfused zones of myocardium in patients with angina pectoris (pts), then specific antiplatelet therapy might improve cardiovascular function and exercise performance. Exercise tolerance (ET) on a bicycle ergometer, heart rate-blood pressure product (HRxBP), and ischemic ECG changes at exercise endpoint were compared before and during oral aspirin (A) therapy (2.4 gms/day for 2 weeks) in 11 normal subjects (nls) and in 10 pts. Platelet aggregation (agg) threshold in response to ADP was measured. Untreated pts had increased platelet aggregability when compared to nls. Mean concentration of ADP for agg was 2.1$\pm$0.3 uM in pts and 4.7$\pm$0.5 in nls ($p<.01$). After A, platelet release of ADP in response to aggregating agents was abolished in both pts and nls, raising the agg threshold significantly. However, no change in ET was observed in either group following A and myocardial oxygen requirements were similar as judged by an unaltered HRxBP in both groups. In pts, total work performed was 866$\pm$122 kpm before and 933$\pm$180 kpm after A, with the onset of angina the end-point of exercise. HRxBP was 16,000$\pm$480 before and 16,300$\pm$500 after A. Exercise induced ischemic ECG changes were not altered by A. Thus, A significantly reduces platelet aggregability in pts with angina pectoris but does not improve ET, change pain threshold or alter ischemic ECG abnormalities. However, the possible benefit of A in prevention and limitation of myocardial infarction has yet to be elucidated.

QUANTITATION OF LEFT VENTRICULAR INTERSTITIAL TISSUE IN LOW CARDIAC OUTPUT SYNDROME FOLLOWING VALVE REPLACEMENT FOR MITRAL INCOMPETENCE

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Low cardiac output syndrome (LCOS) is frequently associated with early death following mitral valve replacement (MVR) for severe chronic mitral incompetence (MI). It has been proposed that the low left ventricular reserve (LV) inherent to the preoperative disease is inadequate to overcome the sudden increased systolic overload caused by the valve made competent at surgery. Twenty-two hypertrophied hearts (HH)(mean weight (MW) 619 gm) free of coronary disease obtained from patients (PTS) who died of LCOS following MVR for severe chronic MI were studied histologically and matched (by age, sex and date of autopsy) with HH (MW 553 gm) from PTS with hypertensive heart disease (HHD) Class I, and normal control hearts (MW 287 gm) from PTS who died of noncardiac causes. From LV basal and apical histological preparations myocardial fiber (MF) hypertrophy was quantitated by measuring the cross sectional MF diameter (average of 20 fibers) and calculating MF sectional surface area (SSA); the proportion of interstitial tissue to myocardium (IT/M) was quantitated by using a computerized, high resolution video/image digiting system. The MF average SSA was similar in the MI-LCOS ($36.1\mu^2$) and HHD ($39.5\mu^2$) groups and significantly higher than in the normal control group ($26.7\mu^2$). The ratio IT/M was similar in the HHD (41%) and normal control (37%) groups, but was significantly increased (59%) ($p < 0.001$) in the MI-LCOS group. This suggests that in chronic MI an increase in LV interstitial tissue may play a role in the development of preoperative severe cardiac failure and postoperative LCOS.

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE (TAPVD): A 5 YEAR REVIEW IN NEW ENGLAND

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In the 11 centers in 6 states of the NERICP during a 5 year period from 1969 to 1973, 72 patients ranging in age from 1 day to 2 years were diagnosed as having TAPVD. 48 patients had TAPVD as their major cardiac malformation with 23 supravardiac, 14 cardiac and 11 infracardiac. Of the 23 with supracardiac, 20 (87%) were diagnosed before correction or death, 17 (74%) underwent operation with 3 (13%) survivors. Of the 14 with cardiac type, 11 (79%) were diagnosed in life with only 2 of 8 (14%) surviving correction. Two patients of the group were palliated by balloon septostomy. Of the 11 with infracardiac type, 8 (72%) were discovered before death or operation with 5 (45%) undergoing correction with only 1 (9%) survivor. 17 other patients had TAPVD as part of more complex malformations, especially asplenia with single ventricle. 7 additional patients were diagnosed as having TAPVD, 5 following catheterization but were proven at either surgery or autopsy as having other forms of heart disease and not TAPVD. In conclusion, of the 48 patients with TAPVD only, 39 (84%) were diagnosed before death, 30 (63%) underwent operation with only 6 (13%) survivors. TAPVD remains one of the most difficult forms of congenital heart disease to accurately diagnose and to successfully correct.

THE ROLE OF MODIFIED EXERCISE TESTING IN REHABILITATION AFTER ACUTE MYOCARDIAL INFARCTION

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To determine the response of convalescing acute myocardial infarction (MI) patients (pts) to simple stress of usual activities, 55 pts in their third post-MI week performed isometric handgrip exercise for 30 sec. at 50% of peak grip and walked 3 min. at 0 grade at 1.5 mph. The energy cost of this exercise was equivalent to that of using the shower, commode, etc.

Results: Isometrics (55 pts): 48 pts had no ventricular arrhythmia during isometrics, 7 pts had only isolated premature ventricular contractions (PVCs). All pts were asymptomatic. The systolic blood pressure times heart rate product (SBP x HR) did not increase by 50% over resting values in any pt. Treadmill exercise (54 pts):

	Total No. of Pts	New ST-T Changes
Angina	8	4 out of 8
PVCs	13	7 out of 13
Neither	33	11 out of 33

PVCs which were unifocal were paired in 2 pts.

	Abnormal Test	Normal Test
SBP x HR>50% Resting	12 pts	17 pts
SBP x HR<50% Resting	10 pts	15 pts

(Abnormal = angina, PVCs, or ST-T changes)

Although the SBP x HR product correlated poorly with the result of the test, activity equivalent to that considered appropriate for these pts was associated with abnormal stress tests in 22 pts. While mild isometrics appear to be well tolerated, it appears to be inferior to treadmill testing as a means of stress testing the pt with recent MI. Carefully monitored treadmill testing is a useful and safe guide to the acute MI pts' suitability to perform ordinary activity after hospital discharge.

LONG-TERM PROGNOSIS IN IDIOPATHIC HYPERKINETIC HEART SYNDROME

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In order to characterize the natural history of the idiopathic hyperkinetic heart syndrome (HKS), a follow-up study of 24 patients (pts) originially studied in this laboratory from 1958-1962 was undertaken. Five pts were lost to follow-up. One patient with complicating severe mitral stenosis had died of congestive heart failure. Of the remaining 18 pts available for follow-up, historical information was available on 9 and complete histories, physical examinations and electrocardiograms were performed on the remaining 9 pts. The follow-up period for this study ranged from 11 to 25 years. Of the total group of 18 pts only one had cardiac symptoms of dyspnea, palpitations or edema at time of re-evaluation. In the group of 9 pts with histories, physical examinations, and electrocardiograms three were symptomatic initially but only one at time of follow-up. Systolic murmurs and/or hyperdynamic heart and pulses initially present in all, disappeared or decreased in 7 and increased in none. The frequency of systolic hypertension decreased from 7 of 9 to 4 of 9 but that of diastolic hypertension increased from 0 of 9 to 2 of 9. EKG abnormalities initially present in 7 of 9 were present in only 2 of 9 at follow-up. Repeat catheterization in the symptomatic patient revealed persistent elevation of cardiac index and systolic ejection rate. Thus it appears from this study that most pts with uncomplicated HKS have an excellent long-term prognosis without progression of disease state.

OUABAIN EXHIBITS DIFFERENT VOLUMES OF DISTRIBUTION IN ADULT AND PUPPY DOGS

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To study why infants are less sensitive to digitalis than adults we gave ^{3}H-ouabain, 0.05 mg/kg, intravenously to 9 adult and 9 seven-to-ten week old puppies. Serial blood samples were obtained for 4 hrs and the animals then sacrificed. Heart, spleen, liver, kidney, skeletal muscle and plasma were then analyzed for ouabain content. Using a linear two-compartment open model and weighting all points with the inverse of the sample variance at each time, measured serum ouabain correlated closely with predicted values (r=0.99). In puppies, volume of distribution (V) of ouabain was 188±3.5 cc/kg (M±SEM) while in adult dogs it was 78±0.4 cc/kg (P<0.01). All kinetic coefficients in the model were not significantly different between puppies and adults. The time constant for the first phase of plasma ouabain was 2.99±0.20 min in adults and 4.56±1.41 in puppies. The slow phase was 36.7±8.3 min in adults and 43.5±8.5 in puppies. Since kinetic coefficients are the same for a given dose per Kg, the same mass of ouabain per Kg is in rapid equilibrium with the plasma, but because of the smaller V in adults, serum ouabain concentration was greater at each time period. In addition, adults had higher tissue ouabain concentration and 8 of 9 developed arrhythmias compared with only 1 of 9 puppies. Therefore, our data suggest that age-related differences in digitalis sensitivity are due, in part, to differences in ouabain V.

CORONARY ARTERY DISTRIBUTION IN PATIENTS WITH PROLAPSE OF THE MITRAL VALVE

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Coronary angiograms were reviewed in 31 patients with idiopathic prolapse of the posterior mitral leaflet. There were 19 males and 12 females, ranging in age from 33 to 69. The coronary artery which supplied the posterior descending branch was designated as dominant (D). There were 27 D right coronary artery (RCA) and 4 D left coronary artery (LCA). Attention was paid to whether the origin of the vessel which courses in the posterior atrioventricular groove (AVG) was from the RCA or left circumflex (LCF). In the D RCA group, the AVG arose from the RCA alone in 6 and from the LCF alone in 1 patient, and in 20 patients, from both. In the D LCA the AVG arose from the LCA in all 4. The frequency of D RCA and D LCA and the origin of the AVG did not differ in the patients with prolapse of the mitral valve from a control group of 30 patients similarly analyzed. In all instances, the AVG arose from either the RCA or LCF, or both. In no case was the AVG branch totally absent. The results of this investigation do not support the thesis, previously advanced by others, that prolapse of the mitral valve is related to absence of the left circumflex coronary artery, but indicate a normal range of variation in coronary arterial distribution.

EXERCISE MYOCARDIAL BLOOD FLOW IN SURGICALLY AND MEDICALLY TREATED PATIENTS WITH ISCHEMIC HEART DISEASE

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In order to evaluate results of coronary artery saphenous vein bypass graft (CASVBG) surgery, 27 successive candidates for CASVBG surgery were studied by cardiac catheterization at rest (R) and during symptom-limited supine maximal exercise (Ex) before and one year following either CASVBG surgery or medical treatment. Myocardial blood flow (MBF) was measured by the N_2O method using gas chromatography. Group I consisted of 13 patients (pts) with > 66% of grafts remaining patent. Group II consisted of 8 pts treated medically and 3 pts with < 50% of grafts patent. No change in myocardial oxygen consumption ($M\dot{V}O_2$), heart rate (HR), HR X blood pressure (BP), or peak LV dp/dt was noted in either Groups I or II at R or in Group II during Ex after one year. Group I pts were able to achieve significantly greater levels of Ex ($_R$ > 0.001), $M\dot{V}O_2$ ($p < 0.02$), HR ($p < 0.01$), HR X BP ($p < 0.001$), and peak LV dp/dt ($p < 0.01$) one year following successful CASVBG surgery. Pts with successful surgery increased exercising $M\dot{V}O_2$ by 5.81 cc/100 gm LV/min during Ex while pts treated medically increased by only 0.54 cc/100 gm LV/min (p=N.S.). HR X BP continued to serve as good predictors of $M\dot{V}O_2$ (r=0.86) in both groups of patients.

A PROSPECTIVE 2-½ YEAR EXPERIENCE WITH ECHOCARDIOGRAPHIC EVALUATION OF PREMATURES WITH PATENT DUCTUS ARTERIOSUS (PDA) AND RESPIRATORY DISTRESS SYNDROME (RDS).

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Left to right (L→R) ductus shunting commonly complicates the course of RDS in prematures. A collaborative study was designed to prospectively and non-invasively assess the magnitude of PDA shunting. We performed 198 studies on 83 patients. Echo measurements included left atrial dimensions (LAD) in the Z and Y axes, aortic dimensions (Ao) and echo determined mean velocity of circumferential fiber shortening (Vcf). The ratio of LAD:Ao (R) was computed for all. 45 children were followed serially; 22 had biaxial LAD. No child was catheterized; 13 were operated on the basis of R value and physical findings. Normal R and VCF for this age and size are .77±(.01 S.E.) and 1.5± (.04) respectively. Institutional data were statistically similar except as noted. For the entire group, VCF=1.86±.04 (P<.01) and R=1.19±.02 (P<.01). For those operated, pre-operative VCF was 2.11±.17. Calif. pre-operative R was 1.06±.07 for 5 patients and Ariz. pre-operative R was 1.7±.15 for 8 patients. After surgery, Ariz. R fell to .96±.05 (P<.01) and VCF decreased to 1.6±.2. It is clear that serial echo determinations of R and Vcf are valuable predictors of the magnitude of ductal shunting, and are useful for selection of patients for operation.

INEFFICACY OF "THERAPEUTIC" SERUM LEVELS OF DIGOXIN IN CONTROLLING THE VENTRICULAR RATE IN ATRIAL FIBRILLATION

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Although therapeutic and toxic serum concentrations of digoxin have been established, there is sparse information permitting correlation of drug level with clinical effect. This study was undertaken to assess the radioimmunoassay serum digoxin levels (DL) in 30 pts with acute atrial fibrillation (AAF, 39 determinations) and 30 pts with chronic AF (CAF, 54 determinations). The chronic fibrillators were subdivided into those who were clinically stable (14 pts), and those unstable with a superimposed illness (16 pts). Slowing of ventricular response (VR) (65 - 95 beats/min) at "therapeutic" levels of digoxin (0.8–2 ng/ml) was achieved in only 5/39 with AAF and 7/38 clinically unstable pts with CAF. However, 10/16 with stable CAF slowed adequately with therapeutic or subtherapeutic DL's. 39 of these were in pts who were ill with conditions such as infection, hypoxia or recent thoracotomy. Slowing of the VR required potentially toxic DL (2.5-6 ng/ml) in 14 instances. Concl; 1) DL's below 2 ng/ml are usually sufficient to control VR in stable pts with CAF; 2) These levels often fail to lower VR appreciably when a complicating illness coexists; and 3) Even high concentrations of digoxin, $>$ 2.5 ng/ml, often fail both to produce adequate AV blockade and to elicit signs and symptoms of toxicity in pts with atrial fibrillation and rapid ventricular response.

MYOCARDIAL LYSOSOMAL HYDROLASES 1 HOUR FOLLOWING CORONARY OCCLUSION: EFFECT OF COLLATERAL BLOOD FLOW

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Early changes in lysosomal enzymes must occur, if their role is significant in irreversible myocardial injury. We therefore ligated the anterior descending coronary artery in 12 dogs and after 60 min excised epicardial and endocardial samples from the ischemic and adjacent normal heart. The muscle was disrupted and fractionated by ultracentrifugation into nuclear pellet (NP) heavy lysosomal pellet (HL), light lysosomal pellet (LL), microsomal pellet (M) and supernatants (S). Electron microscopy demonstrated changes characteristic of ischemia in tissues and sedimented fractions. Acid hydrolase stains indicated abundance of residual bodies in the HL fraction and membrane bound material in the LL fraction. Significant decreases in the specific activity (μ moles/mg-min) of N-acetylglucoseamindase (NAG) and β-Glucuronidase (β-GLUC) occurred in the endocardial LL fraction: (NAG from .64 to .45, β-GLUC from .80 to .41, $p<.005$), while increases in both were found in supernatants (NAG from .46 to .62, β-GLUC from .56 to .70). Losses of p-nitrophenylphosphatase occurred in both LL and S (from 2.10 to 1.50 in LL, from 1.30 to 1.08 in S, $p>.01$). Moreover, a decrease of NAG in HL was positively correlated to the degree of ischemia, measured with radioactive microspheres ($r = .9$, $p<.001$) and the enzyme appeared normal when collateral flow (CF) was 40%. CF in endocardial samples averaged 19% of control. Ischemia and enzyme changes were less significant in epicardial samples. The early loss of enzymes from the lysosomal fractions in severe ischemia strongly suggests a role for lysosomal hydrolases in the necrosis that follows coronary occlusion.

THE VALUE OF ECG TELEMETRY IN DETECTING ARRHYTHMIAS DURING THE CONVALESCENT PHASE OF ACUTE MYOCARDIAL INFARCTION.

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In recent years large amounts of time and money have been spent in equipping progressive coronary care units with ECG telemetry (T) equipment, and in training personnel to interpret arrhythmias (A). Currently many hospitals are monitoring the ECG rhythm of patients convalescing from acute myocardial infarction (MI) after their transfer from the CCU. Others are making plans to do so. However, the value of this approach to patient care has not been established. Therefore, we assessed the value of T in a group of 100 patients recovering from acute MI after their transfer from the CCU. The patients' ages covered a span of the 4th through the 9th decade. There were 73 men and 27 women. Patients were monitored from 1 to 15 days, mean, 4 days. Arrhythmias were detected in 66/100 patients (66%), 46% detected within the first 2 days. Thirty-eight patients (38%) had PVCs, 2 had ventricular tachycardia, and 3 had ventricular fibrillation (VF). In 27/66 patients with A (41%) treatment was changed as a direct result of T. In 1 case T was life saving. Three patients died who had experienced irreversible brain damage as a result of VF prior to CCU admission, and 1 died secondary to ventricular rupture. There were no complications attributable to A in any patient in whom no A was observed by T. T also detected early digitalis toxic A in 1 patient. Because of the 41% rate of change in therapy due to A detection with T, T is of value in treating patients recovering from MI.

SALUTARY EFFECTS OF EXTERNAL COUNTERPULSATION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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To determine whether external counterpulsation (ECP) protects myocardium we studied 13 patients with myocardial infarction treated with ECP, 13 conventionally managed patients matched for estimated infarct size and 13 normal subjects. Ventricular premature complexes (VPCs) on 20 hour continuous ECG recordings were quantified with the Argus/H computer system. Infarct size was predicted from projected serum CPK values on best fit curves derived from early CPK values as previously described. Observed infarct size was estimated from 48 hr serial CPK changes. ECP was performed for 30 min with 15 min rest periods for 18 hrs beginning as soon as infarct size had been predicted. It augmented intra-arterial diastolic pressure by at least 30 mm Hg in all patients. ECP did not release substantial amounts of CPK from skeletal muscle in normal subjects (mean peak CPK = .067 IU/ml). ECP decreased the frequency of VPCs within one hr in all but one patient (av. decrease from 160 to 89 VPCs/hr, $p<.01$), with the reduction persisting throughout the 20 hr recording interval. VPC frequency remained constant in controls during corresponding intervals (av. increase = 2 VPCs/hr). Although ECP decreased pulmonary artery occlusive pressure (mean decrease = 7 mm Hg), it did not preserve jeopardized myocardium. Average predicted and observed infarct size were similar (91 and 90 CPK-g-eq) in treated patients, as well as in controls. In three patients treated with ECP, frank extension of infarction (averaging 134%) accompanied termination of the intervention. Thus, ECP decreases the frequency of VPCs after infarction. However, although it may slow the evolution of infarction, it does not salvage ischemic myocardium.

DETECTION OF REGIONAL MYOCARDIAL DYSKINESIA BY ECG-GATED, COMPUTERIZED RADIOISOTOPE ANGIOGRAPHY

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An ECG-gated, computerized method of radioisotope angiography recently developed in this laboratory was used to evaluate regional myocardial dyskinesia in ten patients who, 2 hours subsequently, underwent routine cardiac catheterization including left ventriculography. This computerized method organizes the scintillation data from 1200-1500 cardiac cycles into an average or typical cardiac cycle, from which the ventricular volume curve, the end-diastolic (ED) scintillation image, and the end-systolic (ES) image can be obtained. A scintillation subtraction (SS) image which depicts the presence, location, and extent of regional myocardial dyskinesia, is constructed by subtracting the ES image from the ED image in a manner that preserves 3-dimensional information (relative volume changes). The SS image was normal in four patients with valvular and/or congenital cardiac lesions and in one patient with coronary artery disease (CAD), all of whom had normal left ventriculograms. The SS image showed definite abnormalities in five patients with CAD; in each case the abnormality was confirmed by conventional contrast angiography and was compatible with the location of an infarct as indicated by ECG. This method of radioisotope angiography can be performed by a technician on an out-patient basis and can be repeated frequently because of a low radiation dose to the patient. Therefore it may offer several advantages over other techniques for investigative as well as routine clinical studies.

PHONOANGIOGRAPHY, A NON-INVASIVE DIAGNOSTIC METHOD FOR EVALUATING ARTERIAL STENOSIS.

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We have evaluated the use of phonoangiography, spectral analysis of vascular sounds, as a method for quantitating the extent of carotid stenosis. The theoretically and experimentally derived relationships between the spectra of bruits distal to a stenosis and the geometry of the lesions were validated clinically with 35 patient studies of the carotid bifurcation. The system used was entirely non-invasive, consisting of a piezo-electric transducer applied to the skin and connected to a semiportable unit containing tape deck, A/D converter and minicomputer with a keyboard and CRT display system. Spectra were analyzed using the relationship fd/U=1 where f is the "break frequency" at which the bruit amplitude falls sharply, d the stenotic diameter, and U the peak systolic flow velocity in the unoccluded region. The non-invasive data were compared with stenotic diameters which ranged from 0.5 to 5 mm and which were estimated by an independent observer from a standard radiographic carotid angiogram. If U was assumed to be 50 cm/sec the stenotic diameters determined by the two methods agreed to within a mean deviation of $\pm$ 0.69 mm. If U was corrected by an empirical constant for bruit intensity, the two methods agreed to within a mean deviation of $\pm$ 0.46 mm. In only two of the cases was the variation between the diameter obtained by the invasive and non-invasive methods more than 1.5 mm.

Non-invasive analysis of arterial bruits can give useful information about the extent of arterial stenosis for preoperative evaluation as well as for longitudinal study of progression or regression of atherosclerotic disease.

ASCENDING AORTA-PULMONARY ARTERY ANASTOMOSIS FOR CYANOTIC CONGENITAL HEART DISEASE.

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Between 1965 and 1974, ascending aorta to pulmonary artery anastomosis(APA) was performed in 206 patients (pts) at our institution. Tetralogy of Fallot(TOF) was present in 106(51%) pts, pulmonary atresia with intact ventricular septum in 27(13%), tricuspid atresia in 24(11%) and complex cyanotic congenital heart disease in 49(25%). In 80/206 pts (40%) the procedure was done in the neonatal period. Mortality rate (death within 1 month of surgery) was 24%(49/206); there were an additional 21(10%) late deaths (average=18 months after surgery). Cardiac catheterization in 77 pts (mean=4 yrs after APA) demonstrated pulmonary artery(PA) hypertension in 12 and kinking of the PA at the site of anastomosis in 8. Congestive heart failure developed after APA in 52/206 pts. It was responsible for 12/49 early and 3/21 late deaths. Inadequate flow through the shunt resulted in 13/49 early and 7/21 late deaths. Further palliative procedures were performed in 42/206 pts (20%). Intracardiac repair performed in 41 pts an average of 4½ yrs after APA, was associated with a mortality of 24%(10/41). The rest of the pts(95/206) are alive an average of 3 yrs after APA and are either awaiting repair or presently inoperable. Among pts with TOF (excluding those with pulmonary atresia) mortality from APA was 34%(18/53) and repair 24%(8/33). However, the mortality of repair in pts with TOF and APA between 1972 to 1974 was 11%(2/19). By contrast, the mortality for one stage repair of TOF in infancy using hypothermia at our institution during the same period is very low (0/15 pts). We conclude that the significant mortality rate and complications of APA may warrant a more aggressive one stage correction when the lesion is amenable to such surgery.

CORONARY OCCLUSION DURING CORONARY ANGIOGRAPHY

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Angiographically documented coronary artery dissection or embolism occurred in 12 of 2500 patients (pts) during coronary angiography. 8 pts. were treated medically, and 4 pts underwent emergency myocardial revascularization. In the medically treated group 5 pts. had dissection of the right coronary artery (RCA), and 3 pts had emboli to the left circumflex artery. 7 of 8 pts developed an acute myocardial infarction (AMI) with ECG changes predicted by the coronary artery involved. All 8 pts. survived. 4 pts. had emergency coronary artery bypass surgery for refractory ventricular fibrillation (VF) (2 pts. with main left coronary occlusion) or because a significant amount of myocardium was thought to be in jeopardy (1 pt with an embolus to the left anterior descending artery (LAD), 1 pt with RCA dissection and severe 3 vessel disease). The time from coronary occlusion to thoracotomy was less than 1 hour in 3 pts. and 3 hours in the 4th pt. 3 of the 4 pts. survived surgery, but all 3 evolved AMI's postoperatively. In 1 pt who had an embolus to the LAD, an AMI evolved postoperatively as documented by ECG changes and ventriculographic evidence of anterolateral akinesis. However, the graft to the LAD was patent as assessed by postoperative angiography.

In patients who sustain coronary occlusion during coronary angiography, AMI was not prevented by emergency coronary artery bypass surgery. It appears that this procedure should be reserved for medically unstable patients with refractory VF or severe hypotension.

EFFECTS OF RATE, ATROPINE AND PROCAINAMIDE ON HUMAN VENTRICULAR REFRACTORINESS

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The effective refractory period of the ventricle (ERP-V) was measured in 25 patients. Right ventricle (RV) was paced at different basic cycle lengths (BCL) and premature beats were introduced at progressively shorter coupling intervals. ERP-V was defined as the longest V_1-V_2 interval when ventricular capture failed. QT interval was taken as approximation of ventricular action potential duration (APD). Mean ERP-V at BCL 600 msec was 244 msec. ERP-V decreased at shorter BCL but ratio ERP-V/QT was constant for each patient, regardless of BCL (0.60 ± 0.3, 84 determinations. In 6 patients given 1 mg atropine (A), the ERP-V did not change in 4 and increased 10% at 1 of 3 BCL tested in the other 2 patients. In 4 patients given procainamide (PA) 500 mg IV, mean ERP-V increased 30%, QT increased 4%. ERP-V paralleled serum PA levels and fell quickly to control values within 30 minutes after PA. Double and triple beating occurred in 5 patients at short coupling intervals, disappeared after PA and reappeared as drug levels fell. These studies show that ERP-V 1) can be safely determined; 2) is directly related to BCL and QT interval; 3) usually is unaffected by A; 4) is prolonged by PA more than is QT suggesting confirmation of in vitro increase in ERP/APD ratio.

POSTEXTRASYSTOLIC POTENTIATION(PEP) AND IMPROVED LEFT VENTRICULAR CONTRACTION IN CORONARY ARTERY DISEASE(CAD). PREDICTION OF POSTOPERATIVE VENTRICULAR FUNCTION

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The present study was to evaluate effect of PEP on myocardial function in CAD and relate these changes to effect of aortocoronary bypass surgery on left ventricular (LV) contraction pattern. Group(Gp) I consisted of 14 patients(pts) with no myocardial infarction(MI) and normal (nl) LV contraction; Gp II (19 pts) had no MI but had LV asynergy; Gp III (17 pts) had MI with LV asynergy. No CAD and nl LV function was present in 12 pts (nl Gp). Quantitative ventriculograms performed resulted in extrasystoles followed by a compensatory pause. End-diastolic, end-systolic(ESV) and stroke volume(SV) and ejection fraction (EF) were determined in the postextrasystolic beat(PEB) and the next beat (control beat). In all Gps the PEB revealed an increase in SV, EF and decrease in ESV as compared to control beat. Gp I and nl Gp revealed no difference, while the decrease in ESV and increase in EF were greater in Gp II and III as compared to nl Gp and Gp I ($p<0.01$). In Gp II and III PEP resulted in no change (7), improved (15) or nl (14) contractile pattern as compared to control beat. Hypokinetic LV wall segments became nl in 22/32 as compared to 6/25 akinetic segments ($p<0.01$). PEP resulted in a normal LV contractile pattern in 13/19 in Gp II and only 1/17 in Gp III ($p<0.001$). In 20/24 pts in Gp II and III the changes in contractile pattern after aortocoronary bypass surgery corresponded to that observed preoperatively in the postextrasystolic beat. This study indicates that PEP can detect residual myocardial function in pts with abnormal LV function and CAD and is useful for predicting postoperative improvement in LV contraction.

LONGITUDINAL EVALUATION OF PATIENTS AFTER CORONARY ARTERY BYPASS BY SERIAL TREADMILL TESTING

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One hundred forty patients (pts) with symptomatic coronary artery disease who underwent coronary artery bypass (CAB) were studied postoperatively by serial multistage treadmill exercise testing (TET). No preop TET was performed in 26% (36/140). Preop TET response was positive (pos) [greater than 1 mm ischemic ST depression] in 69% (72/104) and negative (neg) in 31% (32/104). Thirty-two pts who had neg TET preop remained neg postop (mean 14.6 months). Of these, 6% (2/32) subsequently converted to pos at 3 and 14 months. Of those pos preop, 32% (23/72) remained pos (mean 13.8 months) while 68% (49/72) had a neg TET postop (mean 8.6 months). Late reversal to pos TET occurred in 20% (10/49) at 23.6 months (mean). In pts with pos TET preop, pressure heart rate product (PRP) improved by 11% (from 233 to 262 $x10^2$) in those who remained pos postop, by 29% (from 219 to 308 $x10^2$) in pts who converted to neg, and by 13% (from 206 to 237 $x10^2$) in pts who reverted to pos. Pts with neg TET preop who remained neg postop experienced a 16% improvement (PRP from 251 to 301 $x10^2$). Maximum heart rate and TET stage increased in similar proportions. The magnitude of mm ST ischemic depression, frequency of extrasystoles and number of grafted vessels did not influence the postop results in TET performance or ischemic response. Serial TET is an excellent noninvasive test in CAB follow-up evaluation. Reversals from early postop neg TET to late pos TET suggest that while CAB may play an important palliative role, it probably does not alter the progressive nature of the disease.

CLINICAL ASSESSMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH AORTIC STENOSIS

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The relationships between aortic stenosis (AS), coronary artery disease (CAD), angina pectoris, and myocardial infarction were studied in 173 patients with calcific AS who had coronary arteriography as well as cardiac catheterization. All were over age 40 and had definite cardiac symptoms; 156 later had aortic valve replacement. CAD with areas of greater than 50% narrowing was present in 37% of those aged 40-59 (25/67) and in 68% of those aged 60-82 (72/106). CAD was present in 64% of those with angina (82/128) compared with 33% of those without angina (15/45). Patients with CAD in the absence of angina were over 60 years of age in 12 of 15 instances, and presented with congestive heart failure (7), dyspnea on exertion(3), effort syncope (4), or complete heart block with syncope (1). Angina which occurred only in association with dyspnea on exertion was associated with CAD in 45% of instances (26/58), whereas angina which also occurred on exertion without any dyspnea, or which occurred with emotional stress, after meals, during the night, or at rest unprovoked was associated with CAD in 80% of instances (56/70). QS patterns in V1-V2 were not correlated with CAD, but pathological Q waves in the inferior and anterolateral leads were associated with CAD in 20/22 instances. Patients with relatively mild AS (valve area 0.55 to 0.80 cm^2/M^2) all had CAD, and in 11/12 instances had angina pectoris as their sole or predominant complaint. A helpful clinical assessment of CAD in patients with AS may be made by taking into consideration the age, the severity of the AS, the presence and type of anginal syndrome, and the evidence of transmural inferior or anterolateral infarction in the electrocardiogram.

THE INFLUENCE OF pH ON LACTATE METABOLISM AND OXYGEN UPTAKE IN CANINE SKELETAL MUSCLE. Alden H. Harken, M.D. Walter Reed Army Institute of Research, Washington, D.C.

All cells have the capacity to produce lactic acid under anaerobic conditions. The liver is responsible for most of the lactate clearance from the blood. Other tissues can consume lactate, however. The purpose of this study was to evaluate the rate of lactate production and oxygen utilization by an isolated canine hindlimb at various hydrogen ion concentrations. A membrane lung perfusion system was established such that blood flow and temperature could be fixed at normal levels. Oxygen, nitrogen, and carbon dioxide (CO_2) gas flows were independently regulated to provide a fixed arterial oxygen content (CaO_2). By changing CO_2 flow and periodic addition of bicarbonate, the pH of the arterial blood was varied between 6.9 and 7.6 at ten minute intervals. Lactate production and oxygen consumption (V_{O_2}) were evaluated in ten 25-30 kg dogs. The mean O_2 delivery (CaO_2 x flow) was between 16.3 ml O_2/min and 20.5 ml O_2/min. Standard error of the mean in each dog, however, was less than 0.4 ml O_2/min. Lactate production was linearly related to pH: lactate produced = 22.5 pH - 162.5 ($r = 0.75$). V_{O_2} (ml/min/kg limb) = 100.1 pH - 643 ($r = 0.866$). Oxygen consumption may be inversely related to PCO_2 : $V_{O_2} = -0.62\ PCO_2 + 124$, but the correlation is less good ($r = 0.729$). Skeletal muscle can produce and consume lactate. The rate of lactate production may be directly related to pH, and may have a homeostatic effect on pH regulation. Oxygen consumption of skeletal muscle also appears critically pH dependent. The dangers of alkalosis on increased O_2 consumption and lactate production during and following cardiopulmonary bypass surgery are evident. Postoperative alkalosis may rank with the well recognized risks of acidosis, and should be avoided.

LEFT VENTRICULAR FUNCTION ASSESSED BY RADIONUCLIDE ANGIOGRAPHY AND ECHOCARDIOGRAPHY IN PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

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We have shown previously that the ejection fraction (EF) determined by high frequency analysis of the time-activity curve of intravenous ^{99m}Tc corresponds to the EF calculated by biplane cineangiography and is independent of assumptions regarding chamber geometry. Therefore, we have compared the radionuclide method to the EF and mean rate of circumferential fiber shortening (Vcf) derived by echocardiography. In 13 of 36 patients (pts) with previous myocardial infarction who had a normal heart size and no wall motion abnormalities (WMA) (determined by heart-motion videotracking), EF by both methods correlated well ($r = .83$, $p < .001$), and there was complete separation between pts with normal and reduced EF. By contrast, in 23 pts with either WMA (15 pts) or cardiomegaly (8 pts), EF by both methods correlated poorly ($r = .45$). Among these 23 pts, 14 (61%) with a reduced EF by ^{99m}Tc (< .52) had a normal EF by echo. Similarly, 11 of these 23 pts (48%) with a reduced EF by ^{99m}Tc had a normal mean Vcf (>1.05 circumferences/sec) by echo. In all pts with WMA and reduced EF by ^{99m}Tc and a normal EF or mean Vcf by echo, the WMA involved the anterolateral left ventricular surface and none had WMA involving the posterior left ventricular surface. Thus, in pts with anterolateral WMA a reduced EF or mean Vcf may not be detected by ultrasound because the plane of the echo beam does not traverse these areas of asynergy. We conclude that echo overestimates EF and mean Vcf in pts with important anterolateral WMA or cardiomegaly, and that EF by ^{99m}Tc is a more accurate method of assessing left ventricular performance in such pts.

TREATMENT OF SEVERE CORONARY ARTERY DISEASE WITH QUADRUPLE AND QUINTUPLE SAPHENOUS VEIN GRAFTS: REVIEW OF ONE HUNDRED CONSECUTIVE CASES

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In order to establish the anatomical criteria, the functional results and the safety of complete myocardial revascularization for severe coronary artery disease (CAD), 100 consecutive patients (pts.) who received four (96 pts.) or five (4 pts.) saphenous vein grafts (SVG) were analyzed. The age ranged from 37 to 75 years with a mean of 56. Males predominated by a ratio of 12 to 1. As an indication of the severity of multiple vessel disease, 28% were in Functional Class IV and left ventricular function was classified as: 47% good, 44% fair, 8% poor. Of the 404 arteries receiving SVG, 23% were totally occluded, 39% had 90-99% stenosis and 38% had between 50 and 90% stenosis. Fourteen pts. had significant obstruction of the left main coronary artery. All 100 patients had SVG to the left anterior descending (LAD); 96 to the right coronary artery; 94 to the obtuse marginal branch of the circumflex (Cx); 78 to a diagonal branch of the LAD and 27 to the distal Cx. Overall mortality was 4% and correlated with severity of disease. Two pts. had fatal myocardial infarction; one neurologic complication and one had fatal arrhythmia. Development of new or deeper Q waves occurred in 12% and only one of these had low cardiac output. Fifteen per cent had minor atrial or ventricular arrhythmias. Follow-up from 8 to 26 mos., postoperative arteriograms and anatomic indications for multiple grafting techniques will be discussed.

EFFECT OF PROLONGED SPACE FLIGHT ON CARDIAC FUNCTION AND DIMENSIONS

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Future space programs call for long duration spaceflight. However, the effect of prolonged weightlessness on cardiac dimensions and function is largely unknown. In order to assess the effect of prolonged spaceflight on the heart, echocardiographic studies were performed pre- and postflight in the Skylab 4 Astronauts. Preflight measurements in the commander (CDR) revealed the left ventricular end-diastolic volume, stroke volume, and mass to be at the upper limit of normal, while those of the scientist pilot (SPT) and pilot (PLT) were increased significantly above the normal range. These findings in the SPT and PLT resemble those seen in trained distance runners. Wall thickness measurements were normal in all three crew members preflight. Postflight measurements were unchanged in the CDR immediately following splashdown and through 68 days postflight. In both the SPT and PLT, however, slight decreases were noted in left ventricular end-diastolic volume (15%), stroke volume (14%), and mass (5%) immediately following splashdown. These decreases persisted through 11 days postflight but had returned to near normal by 31 days following splashdown. Wall thickness measurements were unchanged. Left ventricular function curves were constructed for the CDR and PLT by plotting stroke volume versus end-diastolic volume during lower body negative pressure. In both astronauts, pre- and postflight data fell on the same straight line demonstrating that no deterioration in cardiac function had occurred. These data indicate that the cardiovascular system adapts well to prolonged weightlessness and suggest that alterations in cardiac dimensions and function are unlikely to limit man's future in space.

THE EFFECT OF GRAM NEGATIVE ENDOTOXIN ON MYOCARDIAL MECHANICAL AND SUBCELLULAR FUNCTION.

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There is currently a great deal of controversy concerning the effect of gram negative endotoxin(GNE) on myocardial contractility. In order to study this effect, four basic preparations were used: 1) the isolated Starling Heart-Lung preparation(HLP),(n=8). 2) HLP's perfused with blood from animals in endotoxin shock(n=8); 3) intact animals(n=8); 4)intact animals with A-V fistula (n=8). Mechanical performance was assessed by following LVEDP and LV dP/dT. Subcellular function was assessed by measuring sarcoplasmic reticulum(SR) calcium uptake and ATPase activity in the whole heart homogenate and the isolated SR. In groups 1 and 2, endotoxin administration(0.05 mg/ml) or perfusion of the HLP with blood from endotoxin shocked animals(5mg/kg) had no effect on the time to spontaneous failure($p > 0.1$). There was no difference in either mechanical performance or subcellular function. Intact animals administered GNE survived 3.9 ± 0.1 hrs and showed no evidence of progressive cardiac failure or any significant difference in the calcium uptake propertities of the SR. In order to enhance venous return, bilateral femoral A-V fistula were produced. This resulted in a significant increase in survival time (8.2 ± 0.6 hrs. vs. 4.2 ± 0.9 hrs. $p < 0.01$). It appears that endotoxin or a product thereof does not possess significant negative inotropic propertities. Further, support of venous return using A-V fistula prolonged survival. This would suggest that GNE effects the peripheral circulation, obviating the need to postulate direct myocardial depression.

CDP-DIGLYCERIDE: INOSITOL TRANSFERASE - A POSSIBLE BETA RECEPTOR

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The physiological effects of epinephrine and CA++ on the heart may be mediated through the metabolism of the phosphatidyl inositols. Radioactive ^{32}Pi labeling of the heart membrane phospholipid, phosphatidyl inositol (MPI), has been shown to be increased by epinephrine in vivo. To investigate the mechanism of this increased labeling, a study of the enzyme responsible for the de novo synthesis of MPI was carried out. The substrate, CDP-diglyceride was isolated from a reaction mixture of CMP-morpholidate and phosphatidic acid. Enzyme activity (in vitro) was measured by following the incorporation of radioactively-labeled inositol into MPI. Rat heart ventricles subcellular distribution studies and enzyme marker analysis localized the enzyme in the 40,000 x g membranous pellet, containing plasma membrane as evidenced by electron microscopy. The enzyme from this fraction demonstrated an absolute requirement for added cation, Mg++ being the most effective. In the presence of optimal Mg++ concentrations, Ca++ was inhibitory. The enzyme was solubilized by sodium deoxycholate. Epinephrine, at a concentration of 1×10^{-5} M stimulated the activity of the solubilized enzyme and changed the apparent K_m(inositol). Propranolol was shown to be competitive with epinephrine. Dibutyryl c-AMP had no effect. These results indicate that the energy requiring synthesis of MPI is directly stimulated by epinephrine, and this stimulation is blocked by propranolol. MPI could then act as a metabolically active cellular membrane Ca++ storage site or membrane permeability effector.

EFFECTS OF ACUTE ISCHEMIA ON REGIONAL MECHANICAL FUNCTION AND ELECTROCARDIOGRAM IN CONSCIOUS DOGS.

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Regional myocardial ischemic injury is generally assessed by electrocardiographic(EKG) or biochemical techniques, while regional function has received less attention, especially in the conscious animal. In order to correlate EKG and functional changes in response to acute ischemia, 6 conscious dogs were studied 3-6 weeks after implantation of occluders and Doppler flow probes around the left circumflex or anterior descending coronary(C) artery for C flow, left ventricular(LV) pressure(P) gauges for overall LV function, i.e., LVP and dP/dt, and 4 pairs of miniature ultrasonic transducers in the subepicardium of the normal, border and ischemic zones(IZ), for segment length(SL), velocity and subepicardial EKG. Prior to release from a 5 min occlusion, overall LV function was slightly depressed, dP/dt/P was 6 ± 1% below control and LV end diastolic P was 4 ± 1 mmHg above control, while function in the IZ was severely depressed as reflected by absent or paradoxical pulsation. The ST segments in the IZ increased by an average of 10 ± 2 mV. By 5 min after release ST segment elevation and C flow had returned to control while IZ velocity was depressed 41% and end diastolic and systolic SL were both significantly elevated. Regional function in the IZ remained depressed up to 6 hours. A 15 min occlusion showed similar rapid return of electrophysiologic changes, but even more delayed return of function. Thus, acute myocardial ischemia induces parallel effects on regional mechanical function and ST segment elevation only during occlusion, but after recovery from even brief periods of ischemia, regional functional derangement persists far longer than predicted from the rapid flow repayment and normal subepicardial electrocardiogram.

POSITIVE INOTROPIC EFFECT OF CHRONIC DIGOXIN ADMINISTRATION IN NORMAL HUMAN SUBJECTS

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There is little information relative to the effects of chronic digitalis administration in normal man. Accordingly, we performed studies in 10 healthy volunteers, aged 22 to 26, after a therapeutic level of digoxin [0.5 to 2.0 ng/ml] had been achieved by oral administration of 0.5 mg of digoxin daily for at least 10 days. Ejection phase indices of left ventricular performance were derived from echocardiographic measurements. Before each measurement, 1.0 to 1.5 mg of atropine was infused to exclude the effect of spontaneous variations in heart rate. For each comparison before and after digoxin, heart rate and systolic blood pressure were matched in each subject. In the resting state after digoxin, the mean rate of circumferential fiber shortening (Vcf) increased from $1.23 \pm .05$ (S.E.) to $1.36 \pm .07$ circumferences (circ)/sec ($p < .03$) [paired t-test]. Similarly, left ventricular internal diameter shortening increased from 35.2 ± 1.4 to 39.3 ± 2.0% ($p < .03$), and the ejection fraction increased from 73.2 ± 1.7 to 76.9 ± 1.9% ($p < .02$). In each subject systemic arterial pressure was raised an average of 40 mmHg by a phenylephrine infusion. Before digoxin, mean Vcf decreased during the phenylephrine infusion to $1.06 \pm .06$ circ/sec compared to $1.18 \pm .06$ circ/sec after digoxin ($p < .03$). Similarly, mean posterior wall velocity decreased to an average of 32.0 ± 2.3 mm/sec before digoxin and to 38.0 ± 1.6 mm/sec after digoxin ($p < .01$). These data indicate that in the normal human subject sustained oral digoxin exerts a potent positive inotropic effect in the resting state and markedly improves cardiac reserve as evidenced by enhanced left ventricular performance during acute pressure overloading.

DEVELOPMENTAL CHANGES IN CARDIAC ACTION POTENTIAL CHARACTERISTICS AND THEIR MODIFICATION BY OUABAIN

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Age related differences in the sensitivity to cardioactive agents and the spectrum of toxic cardiac arrythmias have been well documented. To further elucidate the mechanisms for these developmental differences, the electrophysiologic properties of canine cardiac Purkinje fibers (PF) were studied using microelectrode techniques. Trans membrane action potential (AP) characteristics of PF from 1-7 day old (N), 4-8 week old (P), and adult (A) mongrel dogs were compared in the control state and after superfusion of the PF by ouabain $2x10^{-7}M$. All PF were stimulated at a 500 msec. cycle length. AP amplitude, duration (APD), resting membrane potential (RMP), and phase 0 upstroke velocity (V_{max}) were significantly greater in A than in N. Values for P were intermediate between the other groups. Following superfusion with ouabain for 25 minutes there were decreases in AP amplitude, APD, RMP and V_{max} in PF from all age groups. The changes were greatest in A and least in N, with P intermediate. There was an increase in the slope of phase 4 depolarization in 10/11 A, 7/16 P, and 0/12 N. From these observations it is evident that there are significant changes in the AP characteristics of PF as age increases from N to A. The modifications of the AP and of phase 4 depolarization by ouabain are also markedly different between the various age groups, indicating a greater sensitivity of the mature conducting system to digitalis. These age related develop mental changes in the AP characteristics and their modification by ouabain, may account for the clinical differences seen in the tolerance of digitalis and the spectrum of toxic arrythmias observed in the infant age group as compared to older children and adults.

EFFECTS OF LIDOCAINE AND VERAPAMIL ON SLOW CHANNEL-DEPENDENT AUTOMATIC DEPOLARIZATIONS IN DEPOLARIZED GUINEA PIG VENTRICULAR MYOCARDIUM

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Extracellular current pulses of 3-5 sec duration applied across two electrically insulated chamber compartments induced rhythmic automatic depolarizations in guinea pig papillary muscles bathed in Tyrode solution. These depolarizations were considered to be slow channel-dependent because: 1) the threshold was about -35 mV, 2) the dV/dt less than 20 V/sec, 3) they were suppressed by low Ca^{++} and Mn^{++}, and 4) enhanced by high Ca^{++} and isoproterenol. Recording simultaneous action potentials from both ends of preparation (length $\leq$ 1 mm) showed homogenous and synchronous activity and thereby virtually ruled out the re-entry mechanism. The automatic depolarizations were not suppressed by lidocaine concentrations ranging from 4-16 µg/ml (8 experiments) and 2 µg/ml verapamil concentrations (3 experiments). However, verapamil concentrations $\geq$ 3 µg/ml depressed the automaticity (5 experiments). The verapamil-induced suppression was partly restored by increasing extracellular calcium concentration from 1.8 to 6.8 mM/l. We concluded that slow channel-dependent rhythmic automatic depolarizations in depolarized ventricular myocardium can be suppressed by moderately high doses of verapamil but not by very high doses of lidocaine. These observations may be pertinent to the treatment of arrhythmias originating in the depolarized myocardium.

EFFECT OF OVERDRIVE PACING ON VENTRICULAR TACHYCARDIA FOLLOWING ACUTE MYOCARDIAL INFARCTION

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Following experimental myocardial infarction, a gradual increase in ventricular automaticity has been thought to precede the late development (4-8 hours) of ventricular tachycardia (VT). In 13 dogs AV block was produced by His bundle ligation and infarction accomplished by balloon occlusion of the left anterior descending artery. An attempt was made to quantitate altered automaticity by serially determining ventricular escape intervals (VEI). Following infarction all dogs exhibited nonsustained VT, mean onset 3 hours. Ten dogs developed sustained VT, mean onset 5 hours. VEI was determined before and at hourly intervals post infarction by means of overdrive pacing at rates of 80-220 beats/min. VEI lengthened with increasing overdrive rates during the control period. Following coronary occlusion (CO), until the stage of sustained VT, the same idioventricular focus returned after discontinuation of overdrive without significant shortening of the VEI. During the stage of sustained VT, the VT focus emerged after overdrive at a shortened VEI that did not lengthen with increasing pacing rate. Intermittently, however, the VT focus was suppressed following overdrive pacing. Under these circumstances, the idioventricular focus escaped at the lengthened interval expected for that pacing rate. If a focus exhibiting enhanced automaticity was responsible for the late VT, it must have been protected from the influence of overdrive pacing. The present study indicates an absence of progressive enhancement of ventricular automaticity to account for the sustained VT which follows CO in the dog.

LEFT VENTRICULAR DYSFUNCTION FOLLOWING CIGARETTE SMOKING IN PATIENTS WITH CORONARY ARTERY DISEASE

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Smoking increases heart rate (R) and arterial pressure (P) and decreases external isometric contraction time (EICT) and pre-ejection period (PEP) in normals. The alteration of systolic time intervals is less well known in coronary artery disease patients. Therefore, determinations of R, P, PEP, EICT, left ventricular ejection time (LVET), and the ratios PEP/LVET and EICT/LVET were obtained in 45 age matched normals (N) and coronary artery disease (CAD) male smokers. The measurements were made before and after smoking two cigarettes in rapid sequence. CAD was confirmed by coronary arteriography for each patient.

Both N and CAD showed slight increases in R and P. Before smoking there was no difference in the ratios between N and CAD ($p > .5$). After smoking PEP/LVET did not change for the normal group (0.310 to 0.299) ($p > .1$). After smoking PEP/LVET increased significantly for the CAD group (0.376 to 0.465) ($p < .05$). Smoking increased the ratio LVET/EICT in the N group (6.72 to 9.28) ($p < .05$). In the CAD group LVET/EICT ratio diminished (6.40 to 5.31) ($p < .05$).

Thus, smoking slightly increased the ventricular function in the normals, but consistently depressed ventricular function in subjects with significant coronary artery disease.

SUDDEN UNEXPECTED CARDIAC ARREST IN PATIENTS AFTER SURGICAL CORRECTION FOR TETRALOGY OF FALLOT

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Complete right bundle branch block (CRBBB) and left anterior hemiblock (LAH) occurring in patients following ventricular surgery may have a significant relationship to the development of complete heart block (CHB) during the late postoperative period especially if transient CHB occurs during the immediate postoperative period. Our purpose is to describe four of 175 patients (Pts) without bifasicular block and transient CHB immediately after surgery who had sudden unexpected cardiac arrest many years after surgical repair for tetralogy of Fallot (TOF). Prior to correction, their electrocardiograms (ECG) indicated right axis deviation (RAD), right ventricular hypertrophy. Postoperatively pulmonic stenosis and insufficiency were present in 1, mild pulmonic obstruction in 1 and slight to moderate cardiomegaly in 2. The ECG revealed CRBBB in 2 and normal QRS duration in 2. Frequent unifocal premature ventricular extrasystoles (PVE) were present in 3 pts with additional A-V dissociation in 1. The sudden event occurred during normal activity in 3 pts and mild exercise in 1. Three pts died immediately, and 1 recovered. This patient's ECG revealed CRBBB with multiple unifocal PVE which decreased in frequency on propranolol therapy. Although CHB cannot be excluded we concluded that the mechanism of cardiac arrest was probably preceded by ventricular tachyarrhythmia. We feel that pts with frequent PVE following ventricular surgery are vulnerable for sudden cardiac arrest and death and antiarrhythmia therapy should be strongly considered.

ON-LINE AUTOMATED ANALYSIS OF PRECORDIAL ST-SEGMENTS: ITS VARIABILITY IN NORMALS AND IN PATIENTS WITH STABLE ST ELEVATION

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A computer program has been developed for rapid on-line analysis of ST-segment (SEG) deviations. The accuracy of analysis and variability of ST-SEGS have been tested in 10 normals and 6 patients with stable ST elevation using a 35 lead precordial jacket. For each lead sampled the ST-SEG onset (J point) of 3 successive QRS complexes was identified and averaged. At the end of a mapping those leads with ST elevation ($\Sigma ST\uparrow$) were summed. The middle QRS for each lead sampled was printed for visual analysis with the ST-onset identified. The time for each mapping averaged 8 minutes. The computer analysis of 1,487 complexes was visually inspected for accuracy of ST-onset identification and there was agreement in over 97%. In 10 normals mappings were consecutively repeated over an average of 83 minutes/patient. The $\Sigma ST\uparrow$ per mapping ranged from 0.15 mv to 2/14 mv. The variability of the ST in sequential mappings was minimal (±0.25mv). In 6 patients with stable ST elevation (1.4 mv - 7.0 mv) mapped an average of 67 minutes/patient, there was no statistically significant change in ST variability in sequential mappings as compared to normals. These findings suggest that this program provides an accurate and reliable method of rapid ST-SEG analysis and may be used to evaluate changes in the extent of myocardial injury.

"SILENT" MITRAL VALVE PROLAPSE. ANALYSIS OF 32 CASES

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Mitral valve prolapse (MVP) was demonstrated by angiography (10), echocardiography (7) and both echocardiography and angiocardiography (15) in 32 patients (pts) in whom neither clicks nor late systolic or pansystolic murmurs were heard or recorded. This represents an incidence of 16% of the "silent" form in our series of 207 pts with MVP. Nineteen were females and 13 males; mean age was 44. Only one pt had rheumatic fever, two atrial septal defect and none Marfan's syndrome. In two siblings in this series, a click was heard in the mother who died suddenly and was shown to have myxomatous mitral valve at autopsy. Chest pain present in 27 was exertional in six, nonexertional in 17 and both exertional and nonexertional in four. Dyspnea was noted in 15, fatigue in 10, palpitations in 13, lightheadedness in eight and syncope in three. The ECG showed ST-T changes in II, III and AVF in 13, in left precordial leads in five and in right precordial leads in two. Ventricular irritability was noted in five and atrial fibrillation in three. Left ventricular end-diastolic pressure was elevated in three. Selective coronary arteriography performed in 22 showed no abnormalities. Left ventriculography displayed prolapse of the posterior leaflet in 13 and of both leaflets in 12. In conclusion, the "silent" form is not an uncommon presentation of the MVP syndrome and should be sought in pts suffering from chest pain, particularly in the presence of a normal coronary arteriogram. Echocardiography is of great value in the diagnosis of "silent" MVP.

ECHOCARDIOGRAPHIC DIAGNOSIS OF LEFT ANTERIOR DESCENDING CORONARY ARTERY DISEASE

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In order to determine the usefulness of echocardiography in the diagnosis of obstructive disease of the left anterior descending coronary artery (LAD) comparisons of coronary arteriograms and echocardiograms were performed on 77 patients (pts) with chest pain syndrome. The arteriograms were analyzed as to the presence or absence of >75% obstruction (obs), in the LAD and the location of such obs, i.e., proximal or distal to the origin of the 1st septal branch. The maximal excursions of the interventricular septum (IVS) and posterior wall of left ventricle (PW) were measured on the echocardiogram in a position below the level of the mitral valve. The ratio PW/IVS was determined and considered to be abnormal (abn) if ≥ 2.5. On the basis of LAD pathoanatomy, pts were divided as follows: Group A-no obs; Group B-obs proximal to 1st septal; Group C-obs distal to 1st septal. The results are:

PW/IVS	Group A(n=36)	Group B(n=19)	Group C(n=22)
<2.5 (nl)	34 (95%)	3 (16%)	20 (91%)
≥2.5 (abn)	2 (5%)	16 (83%)	2 (9%)

The sensitivity of abn PW/IVS for detection of LAD obs proximal to 1st septal was 83% with specifity of 80%. Only 3/57 (5%), of pts with normal PW/IVS had such pathology. Thus PW/IVS is a useful parameter for the diagnosis of LAD obs proximal to the 1st septal. However, since PW/IVS was normal in 95% of those without LAD obs and in 91% of those with obs distal to the 1st septal, PW/IVS is not useful in distinguishing these two groups.

RADIOIMMUNOASSAY OF SERUM MYOGLOBIN IN ACUTE MYOCARDIAL INFARCTION

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Rapid documentation and diagnosis is fundamental in the management of patients with AMI. Though at times non-diagnostic, the principle tests for AMI are serum enzymes and ECG changes. AMI can be documented 2-18 hours post-onset of symptoms by the utilization of a radioimmuno-assay (RIA) for serum myoglobin (SMb). The RIA is sensitive to 3.9 ng/ml and is specific for human myoglobin in serum. The normal SMb range was determined by taking blood samples from 150 normal subjects of varying age, sex and race. The normal SMb range is 3.9-88 ng/ml (mean 20.9 SD ± 23.3). 20 normal subjects were studied pre, post and 4 hours post exercise stress test to determine SMb variation following exercise. The mean 4 hour post value was 19.4, SD ± 21.2; no significant difference from control group. SMb variation due to IM injections was studied in 5 subjects who were given 10 cc normal saline injections. Blood samples were taken every hour for 6 hours and none were found to have elevated SMb levels. 50 patients admitted to ICCU for suspected AMI were studied. SMb samples were drawn every hour for the first 6 hours, every 3 hours for the next 12 hours, and every 24 hours for the following 3 days. 30 patients had documented AMI. 20 patients showed no evidence of AMI. SMb levels were significantly elevated in all 30 patients with documented AMI (P 0.001). The peak SMb range was 216-6800 ng/ml (mean 1354). The peak SMb level occurred between 9 and 12 hours post-onset of symptoms. Patients showing no evidence of AMI all had normal SMb levels with a range of 2-88 ng/ml (mean 32 SD ± 22.1). The specific and sensitive RIA for SMb provides a new diagnostic tool for early documentation of AMI.

DIABETES AND CARDIOVASCULAR DISEASE: THE FRAMINGHAM STUDY

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The relation of impaired glucose tolerance to 824 cases of cardiovascular disease evolving over 18 years in the Framingham cohort of 5209 men and women was explored. In 143 men and 153 women who developed "diabetes" there was at least a doubled incidence of cardiovascular events. No critical value of glucose was identified. The impact of diabetes in women was distinctly more pronounced than in men, particularly for brain infarction and congestive failure. Among diabetics the relative immunity of women to cardiovascular disease was virtually obliterated.

The relative impact of diabetes was greatest for intermittent claudication and least impressive for coronary heart disease. Diabetes not only increased susceptibility to cardiovascular events, but once they occurred they were more likely to be fatal.

Multivariate analysis revealed that no more than 20-30% of the effect of diabetes on cardiovascular disease is attributable to associated atherogenic risk factors, although the effect is more potent when accompanied by these. The factor of increased risk of congestive failure in diabetic women was 5-fold. The increased risk of congestive failure was not a product of atherogenic traits which accompany diabetes or interim coronary events and all of the increased risk was confined to those treated with insulin suggesting some form of diabetic cardiomyopathy.

EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL (CANNABIS) ON CARDIAC PERFORMANCE UTILIZING SYSTOLIC TIME INTERVALS

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Systolic time intervals (STI) were measured in 10 healthy male volunteers (ages 22-30) before and after intravenous administration of 25 μg/Kg delta-9-tetrahydrocannabinol (Δ-9THC). STI and blood pressure (BP) were recorded with the subjects supine in a fasting basal state before and 5, 7, 10, 15, 30, 60, 90, and 120 minutes after Δ-9THC administration. Left ventricular ejection time and total electromechanical systole were both corrected for heart rate (HR) as $LVET_c$ and $Q2_c$. Peak postdrug responses were used for comparison of STI.

Mean ± SEM HR before and after Δ-9THC was 62 ± 1 and 94 ± 8 beats/minute ($p < .001$). Mean ± SEM systolic blood pressure in millimeters of mercury (mmHg) before and after Δ-9THC was 120 ± 3 and 127 ± 5 (NS). Mean ± SEM diastolic blood pressure before and after Δ-9THC was 77 ± 4 (NS). Mean ± SEM STI in milliseconds before and after Δ-9THC were respectively: $Q2_c$ 547 ± 3 and 564 ± 4 ($p < .01$); preejection period (PEP) 114 ± 3 and 95 ± 5 ($p < .01$); $LVET_c$ 408 ± 2 and 432 ± 4 ($p < .001$). Thus, Δ-9THC significantly increased HR, shortened PEP and prolonged $LVET_c$ without any change in afterload. These findings suggest augmentation of cardiac performance which could be a direct effect of Δ-9THC, or secondary to endogenous catecholamine stimulation.

DEFINITION OF CORONARY FLOW DISTRIBUTION BY CONTINUOUS INFUSION OF KRYPTON-81m

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Krypton-81m (^{81m}Kr) is a radionuclide with a 13 second half-life that emits a 190 keV monoenergetic gamma ray and is an isotope of an inert, diffusable noble gas. We have been able to generate ^{81m}Kr at a constant rate from rubidium-81 by using a miniaturized generator which attaches to the hub of a small (I.D. 0.4mm) Teflon catheter which in turn can be threaded through a standard 7 or 8F angiographic catheter. When infused at constant rate into an artery ^{81m}Kr perfuses an organ in proportion to blood flow and proximity of injection site. Because of its short half-life, delivery and decay reach equilibrium within 2 minutes and the amount of radiation measured in any area is proportional to perfusion of that area. Persistance of radioactivity due to delayed washout in areas of decreased blood flow does not occur and scans can be repeated at short intervals. Radiation hazard to the patient and environment is negligible. In preliminary studies, using a digital data disc and color video display subtraction system, it has been possible in open-chested dogs to obtain sequential high resolution scans which show the flow distribution of the left coronary artery and its branches and the immediate effect of arterial occlusion. The unique features of this radionuclide suggest that intracoronary infusion of ^{81m}Kr might, in conjunction with angiography, define more accurately areas of altered myocardial perfusion and thereby significantly improve the application and evaluation of myocardial revascularization procedures.

SURGERY FOR DISCRETE AND DIFFUSE SUPRAVALVAR AORTIC STENOSIS.

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Among 188 patients operated upon for various types of congenital aortic stenosis (AS) at Children's Hospital Medical Center, there were 15 with supravalvar AS. Nine of these patients had discrete obstructions. These were treated by insertion of a patch across the stenotic site in 8 patients. There was one operative death. A substantial gradient reduction was demonstrated in 4 of 5 patients re-catheterized post-operatively.

Repair of diffuse hypoplasia of the aortic annulus and ascending aorta (AA) is difficult. Of the 6 patients with this unusual form of obstruction, 3 died following an exploratory cardiac operation. In one of the surviving patients, a 23 year old male with angina, syncope and a peak systolic ejection gradient across the left ventricular outflow tract of 156 mmHg, a newly developed prosthesis was interposed between the left ventricle and descending aorta. The outflow portion of this metal conduit was coupled to a segment of Dacron graft containing a glutaraldehyde preserved xenograft valve. Post-operatively, cardiac catheterization revealed a normal pulmonary artery pressure and cardiac index. The majority of the injected contrast material was seen to pass through the prosthesis into the descending aorta. The patient remains well and markably improved 4 months following operation. In discrete supravalvar AS current surgical technique is satisfactory. For the more difficult diffuse obstruction, a unique surgical method is presented.

PERICARDIAL EFFUSION IN MYXEDEMA: INCIDENCE, BIOCHEMICAL AND CLINICAL CORRELATIONS AND RESPONSE TO THERAPY.

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Pericardial effusion (PE) is a recognized accompaniment of myxedema. Its incidence is unknown, primarily because of past difficulties in establishing the diagnosis. We have studied 33 hypothyroid individuals by echocardiography, an accurate and sensitive method of demonstrating the presence of PE. Ten of the 33 patients (30%) had positive echos for PE. Eight of the ten patients had enlarged hearts on chest x-ray. Of the 23 patients with negative echos five had cardiomegaly. Serum concentrations of thyroxine, 1.8±0.3 vs 1.5±0.1 mcg/dl and of TSH, 34±4 vs 38±5 μU/ml were not different in the groups with or without PE, respectively. However, the end-organ effect of the hypothyroidism appeared to be more severe in the PE group in that this group had significantly slower heart rates on EKG than those without PE: 53±8 vs 68±2 beats/minute, $p<0.05$. Low voltage was present in 5 of the 10 PE patients and 5 of the 23 non-PE patients. None of the patients with PE developed tamponade. Six of the patients with PE were restudied after periods of thyroxine replacement therapy ranging from 6 months to 2 years. All were euthyroid and had negative echos on followup, but two still showed cardiomegaly on chest x-ray (both had associated coronary artery disease). Conclusions: PE occurs in about 1/3 of patients with myxedema. Cardiomegaly on chest x-ray and low voltage on EKG are not reliable indicators of PE. Tamponade is uncommon and the effusions disappear with thyroid replacement therapy.

PARTICIPATION OF THE ADRENAL MEDULLA IN VENTRICULAR FIBRILLATION AFTER ACUTE CORONARY ARTERY OCCLUSION: Gerald J. Kelliher, Ph.D. Andrew Beasley, Sc.D. and Jay Roberts Ph.D. Depts. of Pharmacology and Anatomy, Medical College of Pennsylvania, Philadelphia, Pa. 19129.

It has been reported that plasma epinephrine (EPI) increases following myocardial infarction and is related to the developement of arrhythmia (AR). The purpose of the present study was to examine the role of the adrenal medulla in this response. EPI values were determined from adrenal vein blood before and after acute occlusion of the anterior descending branch (LAD) of the left coronary artery in α-chloralose anesthetized cats. Acute occlusion produced ventricular AR within 5 min in all cats; a 4-fold increase in adrenal vein EPI was noted. Approximately 40% of the animals died in ventricular fibrillation (VF) in the first hour after occlusion. Bilateral ligation of the adrenal veins in another series of animals prevented the development of VF but not AR. Surgical denervation of both adrenal glands 10 days prior to the experiment as well as pretreatment with practolol or sotolol 15 min prior to coronary occlusion prevented the increase in adrenal vein EPI and VF produced by coronary artery occlusion in the control series. Administration of isoproterenol 2 min after coronary artery occlusion to animals with both adrenal veins ligated produced VF in 6 of 7 animals. The data show that adrenal medullary secretions are involved in the occurence of VF after acute occlusion of the LAD coronary artery but do not seem to affect the incidence of other less ominous ventricular AR. Furthermore, our results suggest that the use of beta receptor blocking agents in the initial stages of myocardial infarction may not prevent ventricular AR but may reduce the incidence of sudden deaths due to VF.

MYOGLOBINURIA IN THE DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

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This study was accomplished to assess the specificity of hemagglutination-inhibition (HI) determination of urinary myoglobin (Mb) in myocardial infarction (MI). Mb was isolated from monkey or human tissue. Mb sheep erythrocyte conjugate was prepared and antisera to Mb was produced in rabbits and goats. This test detects concentrations as low as 0.6 ug/ml. Aliquots of urine from 39 patients (pts.) with suspected MI were studied from HI. Serial serum enzyme and electrocardiogram were used for definitive diagnosis of MI. Of 24 patients with documented MI, 15 had at least one positive HI study (63%). Ten of 13 patients with MI (77%) who were studied within 24 hours of the acute event had positive reactions in the infarct group decreased sharply after 24 hours, giving results of 38%, 31% and 25% positivity on days two, three and four, respectively. None of the 15 patients without infarction had positive tests. This test appears to be a sensitive, specific, non-invasive technique in rapid screening of patients with possible acute myocardial infarction during the early stage of symptomatology.

MITRAL VALVE PROLAPSE SYNDROME (MVPS): LEFT VENTRICULAR FUNCTION AND MYOCARDIAL METABOLISM

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The frequent association of arrythmias, electrocardiographic abnormalities, and chest pain in patients (pts) with MVPS, led us to look for evidence of left ventricular (LV) dysfunction and myocardial ischemia in 35 angiographically documented MVPS pts. who were symptomatic and and had normal coronary arteries. Their mean age was 35 years and 27 were women. Varying degrees of LV dysfunction was seen in a majority of the pts. (2/3), as indicated by depressed ejection fraction, diminished contractility and cardiac indexes and elevated pre-ejection period/LV ejection time (PEP/LVET), LV end-diastolic pressure and end-diastolic volume. Twelve pts. had hypokinetic segments by a quantitative segmental wall motion analysis performed from tracings of LV cineangiograms. To investigate the role of myocardial ischemia, metabolic responses to rapid coronary sinus pacing to the point of chest pain or for 10 minutes, were studied in 17 consecutive pts. with chest pain. Seven pts. showed myocardial Lactate production accompanied by chest pain and 2-4 mm ST depression. No correlation was found between the metabolic, hemodynamic and LV abnormalities. However the data does point to significant myocardial dysfunction in MVPS. The ability to elicit chest pain, ECG and metabolic changes with pacing is suggestive of myocardial ischemia and merits further evaluation.

PRESERVATION OF ENDOCARDIAL BLOOD FLOW DURING ISCHEMIA BY PERHEXILLINE

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Perhexiline (P) has been demonstrated to be effective in clinical trials in relieving angina but its mechanism of action has remained obscure. We have investigated P using on a canine preparation in which coronary flow was controlled by a pump and regional myocardial blood flow measured by radioactive microspheres (15±5μ). Measurements were made during control (C) following graded ischaemia (I) and repeated following administration of P (0.2 mg/kilo/min for 10 minutes (CP, IP)). Following administration of P at a constant coronary flow, coronary perfusion pressure increased (C = 126/88, P = 160/121, $p < 0.05$) without a change in systemic pressure. Endo:epi ratios: C = 0.97±.06, CP = 1.10±.14, I = 0.41±.07, IP = 0.64±.13. Coronary flow during C = 118±8, CP = 98±10, I = 27±5 ml/100 g/min. Measurement of MVO_2 and lactate extraction during ischaemia indicated reduced MVO_2 and increased lactate extraction following P at compafable levels of coronary flow. These data suggest that P acts primarily as a coronary vasoconstrictor with the major site of this action being the epicardium. This effect was independent of autoregulation as it persisted during ischaemia. When maximum vasodilatation was present.

INTRAPERICARDIAL AORTA-PULMONARY ANASTOMOSIS FOR PALLIATION OF CYANOTIC CONGENITAL HEART DISEASE

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Some dissatisfaction with the results of the intrapericardial aorta-pulmonary shunt has recently been expressed. We adopted the intrapericardial aorta-right pulmonary artery anastomosis for palliation of cyanotic infants in 1967. A review of our cases employing the intrapericardial technique since that time has shown that there were 16 deaths in 91 patients; a surgical mortality of 17.6%. Six operative deaths occurred in 52 patients with tetralogy of Fallot; a mortality of 11.5%. For tricuspid atresia, three deaths occurred in 17 cases, 17.6% mortality; in transposition of the great vessels, two deaths occurred in eight cases, 25% mortality. There were five deaths in the 14 children with hypoplastic right hearts, truncus arteriosus or pseudotruncus.

Neonates tolerate operation extremely well (2 deaths, 15 cases, 12.3% mortality). The overall mortality for children under one year of age is 23.6% (16 deaths, 68 cases). There were no deaths in the 23 children over one year of age. Fifteen children have had closure of the shunt at the time of total correction with no morbidity or mortality related to the shunt. We still feel that this shunt is the operation of choice for palliation if shunt size is carefully controlled using microscopic surgical techniques.

SURGICAL TREATMENT OF UNSTABLE ANGINA PECTORIS: RESULTS IN 65 PATIENTS

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Sixty-five patients with unstable angina pectoris evaluated using strict criteria had aorto-coronary bypass grafts (saphenous vein) during a 36 month period (September 1971 to September 1974). The mean age of the patients was 53 years, and 92% were males. Twenty-nine (45%) had a previous myocardial infarction and 15 (23%) had symptoms of congestive failure. The mean (±SEM) duration of unstable angina (onset to admission) was 33 ± 4.3 days. Thirty-four patients had three vessel disease (including 10 patients with >70% left main stenosis), 21 two vessel disease, and 10 single vessel disease. Thirty-nine of 62 patients (63%) had one or more areas of left ventricular asynergy. The mean time from admission to catheterization was 4.0 ± 0.35 days and from catheterization to operation 10.4 ± 2.0 days. The patients were treated with coronary vasodilators and/or propranolol during this period, and if EKG or enzyme evidence of infarction occurred, surgery was deferred. Twenty-two patients received three grafts, 29 two grafts, and 14 single grafts. There were no hospital deaths. There have been four late deaths. Three were sudden and presumed to be of cardiac origin. There were nine postoperative infarctions (14%), and there has been one non-fatal infarction in the mean followup period of eight months. Sixteen of 32 patients followed more than six months are free of angina, eight have less angina, and eight are unchanged or worse. This management program of medical therapy followed by operation on a semi-elective basis has minimized hospital mortality and morbidity and may represent the most rational approach to the management of unstable angina.

ELECTROPHYSIOLOGIC AND ELECTROCARDIOGRAPHIC (ECG) OBSERVATIONS IN PATIENTS WITH L-TRANSPOSITION OF THE GREAT ARTERIES (L-TGA). Ehud Krongrad MD, Brian F. Hoffman MD, Frederick O. Bowman,Jr. MD, James R. Malm MD, and Welton M. Gersony MD.
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Five patients (pts) aged 8 to 21 years, underwent surgical correction for L-TGA and associated intracardiac defects. All had dextrocardia, ventricular inversion, and ventricular septal defects (VSD). In all 5 pts. bipolar electrograms of the specialized A-V conduction system (SA-VCS) were recorded through an exploring electrode probe during open heart surgery. In contrast to other pts. with congenital heart disease (CHD), His bundle electrograms (HBE) were not found in the right atrium between the coronary sinus and the membranous septum. HBE were recorded in 4 pts. superior and anterior to the VSD. In one individual, HBE were recorded in a muscular band separating two VSDs. In the pts. studied, His bundle amplitude (HBA) was similar to HBA in pts. with other CHD. In 4 pts. a right-sided ventriculotomy resulted in minimal changes in the QRS morphology, and no prolongation of the QRS complex. Four of the 5 pts. are alive and are in normal sinus rhythm.

Our observations suggest that in pts. with L-TGA: (1) The HB is completely intraventricular; (2) A right-sided ventriculotomy does not cause a right bundle branch block pattern on the ECG; (3) The intraventricular conduction system of the right-sided ventricle may have a left ventricular arrangement; and, (4) That successful surgical repair without injury to the SA-VCS can be accomplished in pts. with L-TGA who require surgical treatment.

IMPROVED RESULTS WITH EPICARDIAL PACEMAKERS: 12 YEARS' EXPERIENCE
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Epicardial pacemakers (EPM) were implanted in 244 patients during the last 12 years. In order to evaluate the advances in epicardial lead (EL) and pulse generator (PG) design, the series was divided into 3 consecutive 4-year periods (groups I, II, III). There were 57 procedures in group I, 162 procedures in group II and 255 procedures in group III. The EL failure rate occurring at less than 2 years after operation decreased from 39% in group I to 9% in group III. PG failure prior to 2 years after placement likewise decreased from 11% in group I to 8% in group III. Long-term survival at 12 years in group I was 79%. One half of the late deaths were not related to the EPM. Group II survival up to 7 years was 88% with only 3% of the late mortality related to the EPM. In the most recent period (group III), EPM related deaths occurred in only 2% of the procedures. Thirty-day mortality was 3% in group III, a decrease from 10% in group I. We have continued to use transthoracic EPM as the procedure of choice when pacemaker placement is indicated.

We currently use General Electric and Medtronic systems. PG failure rates are 2% and 10% respectively. EL reliability for General Electric and Medtronic is identical.

ANTIARRHYTHMIC AND UNDERLYING ELECTROPHYSIOLOGIC PROPERTIES OF PROPRANOLOL IN CANINE ACUTE MYOCARDIAL ISCHEMIA
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To examine the antiarrhythmic and underlying electrophysiologic properties of propranolol in the in situ heart, 14 dogs with acute myocardial ischemia were studied. Temporary (15 min.) ligations of the left anterior descending coronary artery were performed. Bipolar electrograms and monophasic action potentials were recorded and effective refractory period (ERP) determined in the ischemic (ISCH) and normal (NL) zones of the heart. Conduction intervals (Q-EG) were measured from the onset of the QRS in a limb ECG lead to the major deflection of the recorded electrograms in ISCH and NL. Control ligations were compared to those in which 40 ug/kg of propranolol was administered intravenously. With propranolol, there were the following statistically significant mean differences: 1) the number of ventricular beats was reduced(15 to 6 beats/min.); 2) Q-EG intervals were prolonged only in ISCH (28%); 3) monophasic action potential duration (APD) was prolonged in both ISCH (12%) and NL (9%); 4) ERP was prolonged in both ISCH (30%) and NL (18%); 5) APD/ERP ratio was diminished in both ISCH (1.39 to 1.19) and NL (1.48 to 1.4). Thus at a time when propranolol has antiarrhythmic actions in curtailing ventricular beats in acute myocardial ischemia, it slows conduction only in ISCH, prolongs APD and ERP in both ISCH and NL, and reduces APD/ERP in both ISCH and NL.

THE ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION FOLLOWING TETRALOGY OF FALLOT REPAIR.
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To assess left ventricular(LV) function in patients with Tetralogy of Fallot(TOF) by a non-invasive means echocardiograms were obtained in 15 patients with TOF, aged 2 years to 21 years immediately before corrective surgery, one day, one week and 6 weeks after repair. Left ventricular internal dimensions were obtained in diastole($LVID_d$) and systole and ejection fraction(EF) calculated. Clinical scores in the respective pre- and post-operative periods were determined. Pre-operative EF for the group ranged from .56-.87(mean =.71); $LVID_d$ was normal in 13 patients and increased in 2 patients with longstanding operative shunts. The mean EF in 7 patients with moderate to large operative shunts($Qp/Qs > 2:1$) was .66. This was less than the mean EF in either the group with no shunts(4 patients, mean EF =.76) or the group with small shunts(4 patients mean EF =.76). In the immediate post-operative period EF was .44-.81(mean =.64). Those patients (6) with low clinical scores had a mean EF of .53 compared with .70 for those patients with good clinical scores. One week after surgery EF ranged from .47 -.88(mean =.71). At 6 weeks EF was .56 -.81(mean = .70). The one patient with a poor clinical score at this time had an EF of .61 and had the lowest EF in the group one week after surgery. By 6 weeks after surgery the $LVID_d$(normalized for body surface area) in those patients with large shunts($Qp/Qs > 2.5:1$) fell from a pre-operative mean of 4.1 cm. to 3.3 cm. The data suggest that LV EF as determined echocardiographically is normal in both the pre-operative patient with TOF and the patient with successful corrective surgery. In addition echocardiographic determination of LV EF correlates well with the clinical status of the patient and is a useful adjunct in managing patients after TOF repair.

CORONARY ATHEROSCLEROSIS IN VALVULAR HEART DISEASE: THE NEED FOR CORONARY ARTERIOGRAPHY

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The need for routine coronary arteriography in patients undergoing cardiac catheterization because of valvular heart disease is the subject of conflicting reports. For this reason, a series of 201 patients primarily catheterized for pre-surgical evaluation of valvular heart disease also had coronary arteriographic studies. The group included 104 females and 97 males, mean age 50.5 years. Coronary artery lesions in excess of 50% were present in 1 or more vessels in 45 of the 201 patients studied (22%).

In 18 of the 45 patients with significant coronary artery disease (CAD), there was no history of chest pain. Three of the 18 had 3 vessels involved and 2 had 2 vessels involved. Nine had luminal obstruction greater than 70%. Evaluation of risk factors, electrocardiograms, and consideration of the site and extent of valvular involvement did not help distinguish these patients with asymptomatic CAD.

Chest pain atypical of angina pectoris was present in 14 and typical angina pectoris present in 13 of the 45 patients with CAD.

In 35 of the 201 patients studied (17.4%), classic angina pectoris was present in the absence of significant CAD.

We concluded that significant CAD exists in an asymptomatic form in many patients with hemodynamically severe valvular disease, and that often it cannot be detected clinically. If, indeed, characterization of coronary disease is an important element in the present assay or in future medical and surgical management of patients with valvular heart disease, these data would support the need for coronary arteriography in the patient over 40 undergoing cardiac catheterization.

HEMODYNAMIC RESPONSES TO SODIUM NITROPRUSSIDE DURING CORONARY ARTERY SURGERY.

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Hemodynamic effects of sodium nitroprusside (N), administered to treat hypertensive episodes, were studied in 8 patients during coronary artery operations. Heart rate (HR), mean arterial pressures (MAP), mean pulmonary artery pressure (MPAP), left and right ventricular filling pressures (LVFP, RVFP), systemic and pulmonary vascular resistance (SVR, PVR), left and right ventricular stroke work indexes (LVSWI, RVSWI), stroke volume index (SVI), and heart rate systolic arterial pressure product (HR x SAP) were assessed before and during intravenous infusion of N (60 to 120 mcg/min). Results:

	Control	N	
HR	68±17.1S.D.	70.5±15.2	N.S.
MAP (mmHg)	121±25.9	95.1±15.4	$p<0.02$
MPAP(mmHg)	21.5±3.4	14.8±3.9	$p<0.001$
LVFP(mmHg)	15.1±3.2	9.4±3.2	$p<0.005$
RVFP(mmHg)	7.3±2.3	5.4±2.7	$p<0.001$
SVRdyn.sec-cm^{-5}	2470±7.6	1845±6.3	$p<0.02$
PVRdyn.sec-cm^{-5}	132±55	103±43	$p<0.05$
LVSWlg.m/m^2	43.0±11.8	39.2±11.5	N.S.
RVSWlg.m/m	5.7±1.7	4.2±1.7	$p<0.01$
SVIml/m^2	29.9±5.9	33±7.7	$p<0.05$
HRxSAP	12215±5117	9923±3487	N.S.
$\frac{dP}{dt}$mmHg/sec	1223±425	1163±465	N.S.

The data suggest that N is an effective agent for treating hypertensive episodes in heart disease during coronary artery operations, as a consequence of the vascular effects of the agent, reducing the impedance to left ventricular ejection.

A SIMPLE INDEX OF THE DIASTOLIC ELASTIC WALL PROPERTIES OF THE LEFT VENTRICLE FROM ANGIOGRAPHIC DATA

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Previous efforts to estimate the non-linear elastic constant of the ventricular wall from pressure-volume data have used either empirically derived indices or rather complex formulations. In this study the search for an index was guided by a simple formulation of the stress-strain equations for a sphere (both thick and thin walled) The results are in a form which permits comparison with other indices of compliance and/or wall stiffness. It is shown, for example, that the slope of the dP/dV vs.P curve is linear but also is sensitive to variations in muscle volume, while V(dP/dV) varies with pressure. Using the slope (K) of the d(stress)/d(strain) vs. stress curve as characteristic of the wall alone, a search was made for an index which was not sensitive to specific cardiac geometry. It was found that for ventricular pressures greater than 10 mmHg, the quantity (V/P)(dP/dV) is predominantly sensitive to variations in K of the wall. This index was then evaluated on data from several published studies.

The inferred values of K are low compared with the results of other investigators. This discrepancy is only partially explained by a different formulation of the constitutive relation.

Using Gaasch's data for Normal, Inappropriate Hypertrophy, Aortic Stenosis, and Congestive Cardiomyopathy patients, mean values of (V/P)(dP/dV) were 3.01 ± .33(SD), 3.79 ± .37, 4.43 ± .94, and 4.33 ± .43, respectively. When compared with the Normal group, P values were less than .025, .025 and .0025, respectively.

The index (V/P)(dP/dV) directly applied seems to afford a measure of wall stiffness over a rather wide range of pressures and volumes. Further a value greater than 3.5 seems to have pathological correlations.

COMPARATIVE HEMODYNAMIC EFFECTS OF MORPHINE, MEPERIDINE, AND PENTAZOCINE FOLLOWING ACUTE MYOCARDIAL INFARCTION IN MAN.

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Little data are available regarding the cardiocirculatory effects of parenteral analgesics in patients (pts) with acute myocardial infarction (AMI). Thus, hemodynamic evaluation was performed over a 45 minute period following intravenous morphine sulfate (MS) 15 mg (10 pts), meperidine hydrochloride (D) 100 mg (9 pts) or pentazocine (T) (10 pts) 60 mg within 72 hours of AMI. MS produced no significant changes ($p>.05$) from control (C) in heart rate (HR) (C = 93 beats/min), mean intra-arterial blood pressure (BP) (C = 91 mmHg), mean pulmonary artery wedge pressure (PAW) (C = 18 mmHg), mean pulmonary artery pressure (PA) (C = 25 mmHg), cardiac index (CI) (C = 2.6 L/min/M^2), stroke work index (SWI) (C = 29 gm-M/M^2), peripheral vascular resistance (PVR) (C = 1642 dyne sec cm^{-5}), respiratory rate (C = 22/min), or arterial oxygen tension (pO_2) (C = 86 mmHg) or A-V O_2 difference (C = 4.54 Vol. %). D similarly produced no significant changes in any of these variables. However, T produced significant alterations 10 min after administration in BP (83→93 mmHg), $p<.01$, PAW (10→14 mmHg, $p<.01$), PA (16→22 mmHg, $p<.01$) and PVR (1710→1947 dyne sec cm^{-5}, $p<.05$). After 45 min PAW and PVR had returned to C but changes in BP and PA persisted. T had no effect on HR, CI, SWI, pO_2 and A-V O_2 difference. Thus, although MS and D had no deleterious effects in AMI, neither did they alleviate elevated PAW pressure. Significantly, because T increases both preload and afterload, actions which augment myocardial oxygen requirements, this agent may exacerbate myocardial ischemia or failure, and thus may be contraindicated in AMI.

MAHAIM FIBERS AS A BASIS FOR A UNIQUE VARIETY OF PREEXCITATION

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This report concerns pathological findings in a 54 year old female with intermittent preexcitation, who died of breast carcinoma. Electrocardiograms (ECG) revealed predominantly normal sinus rhythm with normal PR and narrow QRS. Episodes of sinus rhythm, short PR, and QRS widening (with delta wave) were also recorded. During preexcitation; QS complexes were noted in leads II, III, AVR, AVF, V_1, and V_{4-6}; R waves were noted in leads I and AVL; and rS complexes in V_2 and V_3. ECG during paroxysmal atrial fibrillation revealed groups of narrow complexes alternating with groups of wide complexes identicle to the anomalous QRS described above. QRS morphology defies classification of this case into any known variety of preexcitation. Complete serial sections were cut through the entire conduction system and both AV rims totaling 18,600 sections. These revealed no bundle of Kent. Instead Mahaim fibers histologically identified as His bundle tissue were given off from the AV bundle both to the right and left sides of the septum associated with the normal fibers of James. The short PR interval is thus explained as produced by James fibers bypassing most of the AV node. Preexcitation appeared to start at the summit of the ventricular septum on both sides and spread anteriorly on both free walls from epicardium to endocardium producing the bizarre ECG. This case revealed that fibers of Mahaim must have the property of conduction; and atrial arrhythmias in WPW are not of necessity caused by reentry but produced by concomitant disease, in this instance carcinomatous atrial involvement.

CONDUCTION SYSTEM IN SUDDEN CARDIAC DEATH

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Sudden cardiac death (SCD) has been attributed to the development of lethal dysrhythmias in coronary heart disease victims, and several recent autopsy surveys showed that 10 to 47% of SCD patients had unsuspected acute myocardial infarction (AMI). The present study concerned histopathologic findings of the conduction system in 49 SCD (within 6 hours of the onset of acute symptoms) patients; 39 with established AMI (Group A) and 10 without (Group B). Both groups showed high incidence of cardiomegaly, significant coronary artery disease affecting two or more vessels, and acute myocardial ischemia undetectable by conventional histological techniques. Stenosis of nutrient vessels of the conduction system was present in about 50% of the atrioventricular (AV) node arteries and about 25% of the sinoatrial (SA) node arteries in both groups of SCD patients. Nonspecific "degenerative" changes (fibrosis, fatty infiltration or both) of the conduction tissue, which might or might not represent results of old ischemic injury, also occurred with similar frequencies. Acute changes (infarction, hemorrhage) of the AV node and bundle branches were found only in two Group A patients, both had massive septal infarction. Thus, the conduction tissue appeared more resistant to ischemic injury and was overtly damaged only on rare occasions in fatal AMI. The scarcity of acute lesions in the conduction system itself suggested that lethal dysrhythmia in SCD was probably due to electrical instability of the acutely ischemic myocardium rather than a direct injury to the specialized tissue of the heart.

ELECTROPHYSIOLOGICAL EFFECTS OF NITROGLYCERIN DURING EXPERIMENTAL CORONARY OCCLUSION

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Previous studies have shown that nitroglycerin (NTG) decreases ventricular premature complexes and increases the ventricular fibrillation threshold after acute coronary occlusion. In order to determine the electrophysiological effects of NTG after occlusion, experiments were performed in 13 mongrel dogs, with heart rate controlled by atrial pacing. Conduction time from the onset of the QRS to local electrogram onset and refractory periods obtained by the extrastimulus method, were determined in normal and ischemic areas of left ventricular myocardium prior to and after variable periods of occlusion, as well as following the IV administration of NTG (300ug bolus followed by an infusion titrated to reduce arterial pressure 20mmHg). Following 15 min of occlusion, refractory periods in the normal area remained unchanged while it shortened in the ischemic area to 82% of control ($p<.001$), creating an 18% mean dispersion of refractory periods. After NTG, refractory periods in the normal area were unaffected while prolongation in the ischemic area to 90% of control occurred thus decreasing the dispersion of refractory periods to 10% ($p<.001$). However, following periods of occlusion $\geq$60 min, NTG had inconsistent effects on ischemic refractory periods, and did not significantly affect refractory period dispersion. NTG had no effects on conduction times of normal or ischemic areas. These observations suggest that 1) NTG enhances the electrical stability of the acutely ischemic ventricle by decreasing the dispersion of refractoriness between normal and ischemic areas in the immediate period following occlusion and 2) NTG has inconsistent effects after more prolonged periods of occlusion.

THE EFFECTS OF GLUCOSE-INSULIN-POTASSIUM THERAPY IN GLOBAL MYOCARDIAL ISCHEMIA

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The metabolic benefits of glucose-insulin-potassium(GIK) administration during myocardial ischemia have recently been questioned as has the proposed clinical efficacy of its use in the management of patients with ischemic heart disease. To test this intervention experimentally in an intact, working swine heart preparation, GIK enriched medium(32.4 mM glucose, .025 units/ml insulin, and 5.9mM potassium)was provided during coronary perfusion in nine control hearts and nine hearts rendered ischemic by reducing total coronary blood flow from 157 to 82 ml/min. In another group of 14 hearts(six control and eight ischemic)coronary perfusate contained 11.8 mM glucose, 5.9 mM potassium, and no insulin. In hearts without GIK, ischemia increased left ventricular end-diastolic pressure ((LVEDP)from 8 to 15 mmHg, $p<.05$)and resulted in declines of myocardial oxygen consumption((MVO_2)from .80 to .68 mmol/hr/g, $p<.05$), free fatty acid(FFA)oxidation(from 31 to 21 µmol/hr/g, $p<.025$), and tissue creatine phosphate ((CP)from 47 to 21 µmol/g). Data for control hearts with GIK were similar to controls without GIK except that glucose uptake was increased to 430 µmol/hr/g. Ischemia had similar effects in GIK-treated hearts(LVEDP:22 mmHg;MVO_2: .51 mmol/hr/g; FFA oxidation: 25 µmol/hr/g;CP;24 µmol/g). Glucose uptake was reduced to 240 µmol/hr/g and average survival time during ischemia was 10 minutes less than in hearts receiving no GIK. These data indicate that in global ischemia GIK provides essentially no metabolic advantages to jeopardized myocardium and suggest any therapeutic benefit derived from such treatment in regional ischemia probably occurs in the uninvolved myocardium.

CLINICAL SETTING AND IMMEDIATE PROGNOSIS OF ATRIAL FIBRILLATION COMPLICATING ACUTE MYOCARDIAL INFARCTION.

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Causative factors, clinical setting and hospital (28 day) mortality were reviewed in 80 consecutive patients (pts) who developed atrial fibrillation (AF) as a consequence of acute myocardial infarction. Pts with AF had a higher mean peak SGOT (130 I.U. vs 107 I.U. $p<0.05$), a higher incidence of pulmonary edema and/or cardiogenic shock (21% vs 12%, $p<0.05$), and a higher mortality rate (35% vs 18%, $p<0.01$) as compared with 720 pts without AF admitted during the same period. Both groups of pts were comparable in age, sex, site of infarction and admission time. The following factors could be considered as predisposing to the development of AF since they were present at the time of appearance of AF: 1. moderate left heart failure (34 pts), 2. pulmonary edema and/or cardiogenic shock (7 pts), 3. pericarditis (10 pts).
AF occurred within the first 72 hours of infarction in 95% of pts and in 20% as a short(<1 hour) single episode. Neither time of onset nor duration of AF were of prognostic significance.
All 15 pts with AF and cardiogenic shock died. Of these in only 3 pts cardiogenic shock preceded AF, whereas in 12 AF preceded the onset of cardiogenic shock. Seven of these 12 died after the first week of infarction. In contrast 85% of pts with cardiogenic shock without AF died within 24 hours of infarction.
Conclusions: 1. AF complicating acute myocardial infarction is associated with larger infarcts, a high incidence of pulmonary edema and/or cardiogenic shock and a high mortality rate. 2. AF can be considered a premonitory arrhythmia of cardiogenic shock of delayed onset.

IMPROVED INTERPRETATION OF SERUM ENZYME ELEVATIONS AFTER CARDIAC CATHETERIZATION BY ANALYSIS OF CPK ISOENZYMES

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Patients with preinfarction angina undergoing cardiac catheterization frequently exhibit elevations of conventionally measured serum enzymes and ECG changes mimicking those seen with acute myocardial infarction. Exclusion of infarction may be particularly important when coronary revascularization is contemplated. Since the MB CPK isoenzyme is relatively specific to myocardium, we assayed CPK isoenzymes in serum samples from 50 patients undergoing left heart catheterization with left ventricular and coronary angiography to determine whether CPK elevations accompanying catheterization can be distinguished from those associated with myocardial infarction. Samples were obtained every two hrs for 24 hrs. Total CPK was assayed spectrophotometrically. Isoenzymes were quantified kinetically and fluorimetrically. Total serum CPK increased in 41 of 50 patients (mean peak = 214 ± 32 (SE) mIU/ml) but MB CPK remained normal (<4 mIU/ml). In contrast, selected samples from 25 patients with definite myocardial infarction and comparable elevation of total CPK (210 ± 40) exhibited increased MB CPK activity as well (26 ± 7). Thus, CPK elevations after catheterization reflect release of enzyme from noncardiac sources rather than from injured myocardium. Furthermore, increased serum MB CPK activity remains a reliable index of myocardial infarction in patients undergoing catheterization.

MITRAL DIASTOLIC MURMURS IN PATIENTS WITH MITRAL PROSTHESES

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Diastolic murmurs with Starr-Edwards mitral valve prostheses have not previously been reported. We have observed five patients (pts.) with such a murmur and each underwent cardiac catheterization and reoperation. Three had significant prosthetic stenosis with an average mean left atrial or wedge pressure of 27 mmHg, a mean cardiac index of 2.46 L/min/M^2, a mean diastolic transvalvular gradient averaging 16.5 mmHg (normal 3 to 8 mmHg) and an average valve area of 0.99 cm^2 (normal 2.0 to 2.6 cm^2). At surgery, all three prostheses were found to be obstructed by thrombus and were replaced.

Two pts. had normal mitral prostheses with cardiac catheterization revealing gradients of 3.3 and 2.3 mmHg and valve areas of 2.1 and 2.8 cm^2. Cinefluorography revealed premature movement of the poppets towards closure. Each had moderately severe aortic insufficiency and amyl nitrate inhalation caused a decrease in the mitral mid-diastolic and presystolic murmurs. Both pts. underwent aortic valve replacement and at surgery the normality of the mitral prostheses was confirmed. Postoperatively, the mid-diastolic and presystolic murmurs disappeared. Cinefluorography revealed disappearance of the premature poppet closure movement in only one of the pts.

It is important to recognize that mitral diastolic murmurs occur with the Starr-Edwards prosthesis and result from either prosthetic obstruction or, in pts. with associated aortic insufficiency, may be Austin Flint murmurs. Clinically, amyl nitrate inhalation may help differentiate between the two, increasing the murmur in those with prosthetic stenosis and decreasing the Austin Flint murmur.

RESULTS FOLLOWING CORONARY ARTERY BYPASS IN PATIENTS WITH LEFT MAIN CORONARY ARTERY DISEASE

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The results of 84 patients (pts) with left main coronary artery occlusion (LMCA) who had coronary bypass (CBP) surgery between Feb. 1971 and Dec. 1973 were analyzed. Class III-IV disability from angina pectoris (AP) was present in 80 (95%) pts and 42 (52%) had unstable AP. There were 2 (2.4%) postoperative (PO) deaths and 3 pts (3.6%) had a PO transmural myocardial infarction. All pts had follow-up (total 1,677 mos; average=20 pt mos; 81% greater than 1 year). At 1 year PO 94% of pts were alive; there were 5 late deaths (at 4, 5, 6, 19 and 24 mos). Of surviving pts; 60 pts are free of AP (80%) and 12 pts have class II AP (88% improved). Pre-op treadmill stress ECG (TSE) was done in 23 pts; 19 (82%) were positive (POS). Thirty-seven pts had PO TSE; 27 were negative (NEG) (71%). Ten of 14 POS pre-op TSE reverted to normal PO. Angiograms were performed in 21 pts PO; 15/50 (30%) CBP were occluded; 8/18 (44%) CBP were patent in 8 pts with AP; 27/32 (85%) were patent in 13 pts free of AP. Five pts had evidence of progressive total occlusion of the LMCA (12/13 CBP were open in this group; 4/5 pts were free of AP and 3/5 TSE were NEG). These data show evidence of improvement in symptoms (AP 88%) and in relief of myocardial ischemia (TSE; 71% NEG PO) in pts with LMCA. In our experience the surgical mortality has been higher in LMCA than in CBP in general (2.4% versus 0.87%). However, survival data suggests increased longevity (4.3 deaths/pt yr, 5.1%) in pts with LMCA who have had CBP surgery (versus expected 11-18%/yr mortality without CBP).

THE INTRAMURAL CORONARY ARTERIES IN HYPERTROPHIC CARDIOMYOPATHY

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The intramural coronary arteries (ICA) have not been examined heretofore in patients with hypertrophic cardiomyopathy. Among 32 such pts studied at necropsy, 20 had left ventricular (LV) outflow peak systolic pressure gradients at rest (Group I), and 12 had no LV outflow obstruction at rest and <30 mm. Hg gradients after provocation (Group II). The ICA were abnormal in 16 of 20 pts in group I and in 8 of 12 in group II. The changes consisted of severe medial hypertrophy (2 pts) and varying degrees of cellular intimal proliferation (22 pts). Most of the latter changes were minimal or mild and in none were the lumens narrowed >50%. The changes were observed in the ICA of the ventricular septum and LV free wall of all 22 pts, but in the right ventricular free wall in only 1 pt. In general, the changes were of greater degree in the pts in group I than in those in group II. Similar intimal changes in ICA were observed in only 2 of 10 adult patients without cardiac dysfunction (controls) and none had medial hypertrophy. The significance of the changes in the ICA in pts with hypertrophic cardiomyopathy is as yet uncertain.

CLINICAL COURSE AND CORONARY ANATOMY OF SUBENDOCARDIAL INFARCTION

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To clarify the clinical course and coronary artery anatomy of subendocardial infarction (SEI), 32 patients (pts) had early coronary angiography (28 within 4 wk of SEI). SEI was defined by 2 of the following: chest pain for longer than 15 min, enzyme elevation, and T-wave inversion for longer than 48 hr. Twenty-four pts presented with unstable angina (AU), and 3 with stable angina (AS); only 5 were asymptomatic. Fourteen had ventricular dysrhythmias, 5 supraventricular dysrhythmias, and 2 bradydysrhythmias; 4 had mild left ventricular (LV) failure. Ten pts had significant 1-vessel disease (i.e. >75% lesion), (4 left anterior descending, 2 circumflex, 1 marginal, 3 right coronary artery [RCA]); 12 pts had 2-vessel disease, and 9 pts had 3-vessel disease. Only 1 pt had mild disease: isolated 90% lesion of posterior ventricular branch of RCA. There were 22 completely occluded vessels in 14 pts. Eight of the 10 pts with 1-vessel disease, 8 of the 12 pts with 2-vessel disease, and 7 of the 9 pts with 3-vessel disease were potentially suitable for saphenous vein grafting. LV end-diastolic pressure was elevated (>15 mm Hg) in 14 pts. Nine pts had normal LV angiograms; 10 pts had hypokinetic segments, 8 akinetic, and 3 dyskinetic. Five pts had generalized reduction in LV contraction; in no pt was LV dysfunction a contraindication for surgery. Early follow-up (5 mo) revealed 23 pts with angina (8 with AS, 15 with AU); only 9 were asymptomatic. Three pts suffered transmural infarctions; there were no deaths. Study showed that SEI is frequently associated with anatomically severe coronary artery disease, is symptomatically an unstable entity, and warrants consideration for early angiography.

MITRAL VALVE PROLAPSE AND CORONARY ARTERY DISEASE: CLINICAL, HEMODYNAMIC AND ANGIOGRAPHIC CORRELATIONS.

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Although prolapse of the posterior leaflet of the mitral valve (PLMV) into the left atrium has been intensively investigated, the frequency of mitral valve prolapse in patients with coronary artery disease (CAD) has not been systematically studied. Among 95 patients with angina pectoris and angiographically proven obstructive CAD prolapse of the scallops of the PLMV was noted in 30. Left ventriculogram in the RAO projection revealed isolated prolapse of the postero medial commissural scallop (PMCS) in 12 patients and the antero lateral commissural scallop (ALCS) in two. Seven patients had prolapse of the PMCS and ALCS, 3 had prolapse of the PMCS and MS (middle scallop) and 6 had prolapse of all three scallops of the PLMV. Left ventricular dilatation with increased trabeculations was observed in 19 patients. Contractility determined in a quantitative fashion by segmental motion analysis was markedly impaired in 29 patients. None of the patients had angiographic evidence of mitral insufficiency. Left ventricular dysfunction was documented in 27 patients by either elevated LVEDP, low CI or decrease EF. In three patients in whom left ventricular contractility improved after aneurysmectomy or aorto-coronary bypass, the previously prolapsed scallops could not be identified in a post-operative ventriculogram. Prolapse PLMV is a frequent angiographic finding in patients with obstructive CAD. Impaired contractility, left ventricular dilatation, and hypertrophy play a significant role in the pathogenesis of this abnormality through distortion of the directional axis of the papillary muscle and changes in the normal spatial alignment necessary for mitral valve closure.

IDENTIFICATION OF THE CONDUCTION SYSTEM IN PATIENTS WITH CORRECTED TRANSPOSITION OF THE GREAT ARTERIES OR COMMON VENTRICLE, TYPE A, AT THE TIME OF OPERATION

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Previously, surgical repair of associated defects in corrected transposition (CTGA)(levotransposition with inversion of the ventricles) or of common ventricle type A has resulted in a high incidence of heart block. Recent pathology studies (Anderson) demonstrated the conduction system in these anomalies to consist of a hypoplastic atrioventricular node which usually makes no contact with the ventricular myocardium, and a second, anteriorly situated node which gives rise to an atrioventricular bundle coursing anteriorly and superiorly along the ventricular septal defect in CTGA, or in the spur of muscle between the pulmonary artery and aorta in common ventricle type A.

Fifteen Mayo Clinic patients (pts) with CTGA (10 pts) or common ventricle type A (5 pts) had electrophysiologic identification of their conduction system at the time of operation. Of the 10 pts with CTGA, 9 had ventricular septal defect, with or without pulmonary stenosis, and 1 had an intact ventricular septum and Ebstein's malformation of the left AV valve; 3 also had isolated dextrocardia.

Electrophysiologic delineation of the specialized conducting tissue confirms recent anatomic descriptions and assisted in avoiding heart block in the majority of cases.

LATE FOLLOW-UP (TO FIVE YEARS) AFTER CORONARY SURGERY IN COMPARISON TO REPORTED MEDICAL SERIES

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Of patients operated between 1968 and 1973, 2669 have been followed with yearly questionnaires. Average follow-up is 2.25 years. Response has been 90% per year return on questionnaires. Data has been tabulated by computer and five year life tables have been constructed for patients based on presence of one, two and three artery disease, or on presence of left main stenosis. Data has been tabulated on relief of angina, number of postoperative infarcts and work status of these patients. Mortality studies have been compared with Wilson's recent summary of world literature on mortality on non-operated coronary patients, most of which had good left ventricular function. Our surgical data is biased unfavorably: It includes the higher surgical mortality of early years and it includes patients with aneurysms, poor left ventricular function, etc. Despite this, five year survival with surgery is impressive. With single vessel disease, surgery and medical survival are comparable. Five year survival with two artery disease is 82% surgical vs. 65% medical. In three artery disease, 73% surgical vs. 51% medical. Most impressive is left main disease, 75% five year surgical survival compared with 29% medical survival. Total postsurgical mortality is 3.1% per year. With present surgical methods these five year results should be improved. For angina, surgery has provided 89% improvement with total or marked relief of pain. Remaining free of further infarct were 91% of patients. In comparison to previous work pattern (working,retired,not employed) over 90% have returned to same category after surgery. Late evaluation indicates surgery is beneficial to clinical well-being and mortality of coronary patients.

THE MECHANISM OF PRODUCTION OF MYOCARDIAL INJURY IN DOGS WITHOUT TOTAL CORONARY ARTERY OCCLUSIONS.

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Acute myocardial infarction can occur in patients without complete occlusion of the coronary arteries. However, in these patients, severe coronary disease is normally present. Accordingly, the goal of this study was to examine the circumstances in which myocardial damage will occur when a coronary artery is partially occluded. In 16 anesthetized open chest dogs flow in the mid left anterior descending coronary artery was reduced by 52±4% (from 25.0±1.5cc/min). This reduction did not cause an increase in ST segment elevation over any of the 12 to 15 epicardial sites in which electrograms were recorded. When isoproterenol was administered(0.15µg/kg/min)(N=10), when arterial hypotension was provoked by bleeding to a mean pressure of 49±5mmHg(N=6), when hypoxia was induced by administration of 10% oxygen(N=8), and when heart rate was increased by atrial pacing to 219±8beats/min(N=6), there was a sudden appearance of ST segment elevation in the area dependent on the reduced coronary flow. The sum of ST segment elevation and number of sites with ST segment elevation > 2mV following these interventions were respectively 49.3±4.5, 77.3±15.5, 47.3±9.7 and 26.3±3.9mV and 7.8±0.6, 9.0±1.0, 7.6±0.6 and 5.0±0.7 sites. When these interventions were discontinued ST segment elevation disappeared within 5 min in all cases. In conclusion, experimentally, myocardial ischemic injury may occur even with only partial occlusion of the coronary artery due to increase in heart rate, reductions in systemic arterial pressure, hypoxia, and inotropic stimulation. These findings suggest that the above conditions may cause acute ischemic injury while coronary arteries are still patent.

ISOSORBIDE DINITRATE AND NITROGLYCERIN FOR THE RELIEF OF CONGESTIVE HEART FAILURE POST-MYOCARDIAL INFARCTION.

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Severe congestive heart failure (CRF) complicating myocardial infarction can be a difficult clinical problem to manage. In this study the hemodynamic and symptomatic response to sublingual isosorbide dinitrate (ISD) (5-10 mg) and nitroglycerin (NTG) (0.4 mg) was evaluated in 8 patients (pts) with CHF post-myocardial infarction. Serial measurements of the pulmonary artery end-diastolic pressure (PAEDP), cardiac index (CI), heart rate (HR), blood pressure (BP), stroke work index (SWI) and total systemic resistance (TSR) were made utilizing a computerized monitoring system.

ISD reduced the initial mean PAEDP from 24 mmHg ±2 (SEM) to 16 mmHg ±1 (P<0.01) at 30 minutes with a gradual return to 24 mmHg ±1 within 4 hours. NTG reduced the initial PAEDP from 21 mmHg ±1 to 14 mmHg ±1 (P<0.01) at 5 minutes with a return to 21 mmHg ±1 by 30 minutes. There were no significant changes in the CI, BP, HR, SWI, or TSR with either ISD or NTG. Two pts with anterior wall aneurysms who had chronic dyspnea at rest despite therapy with digitalis and diuretics were begun on ISD every 4 hours and experienced a relief from their dyspnea and became ambulatory prior to surgery.

These studies have demonstrated: 1) Sublingual isosorbide dinitrate and nitroglycerin reduce the PAEDP in pts with CHF post-myocardial infarction without compromising left ventricular performance; 2) Sublingual isosorbide dinitrate every 4 hours reduces the PAEDP and relieves the dyspnea in pts with CHF; 3) Sublingual isosorbide dinitrate is an effective intervention in the management of CHF post-myocardial infarction.

COMPARATIVE RIGHT-LEFT HEART FUNCTION IN ISOLATED PRESSURE OR VOLUME OVERLOAD

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RV and LV function was tested in children without cardiac failure: 23 atrial septal defect (ASD), 19 patent ductus (PDA), 15 pulmonic stenosis (PS), 10 aortic stenosis (AS). Angiographic maximal volumes of RV, LV and LA were compared with predicted normal (PN) using age, height, weight, heart rate as variables. Angio Qrv and Qlv correlated with Fick Qp,Qs (r=0.65 to 0.94); in PS and AS, Qrv and Qlv were similar (r=0.96, 0.98). Ejection fractions of RV and LV were normal. The following volume data are expressed as % of PN. In ASD: RV-196% (p<.0005); LA-130% (p<.001); LV-83% (p<.005); Qlv-88% (p<.01); Distensibility of RV (Drv)-142% (p<.01); Dlv-87% (p=n.s.). In PDA: LV-158% (p<.005); LA-154% (p<.0005); RV-124% (p<.005); Drv-93% (p=n.s.); Qrv-102% (p=n.s.). In PS: RV-125% (p<0.05); Drv-95% (p=n.s.); LA-105% (p=n.s.); LV-113% (p=n.s.); LV mass (Mlv)-98% (p=n.s.). In AS: LV-89% (p=n.s.); LA-122% (p<0.025); RV-98% (p=n.s.); Mlv-133% (p<.025); Dlv-73% (p<.005); Drv-82% (p=n.s.). The response to volume overload by the contralateral RV or LV differs: in ASD, LV becomes small and Qlv is reduced, while in PDA RV tends to become large. The response to pressure load by the ipsilateral RV or LV also differs: in PS, RV tends to become large when the stenosis is not severe, while in AS, LV tends to become small. Shunt localization and ventricular distensibility influence these changes.

CARDIAC ARREST DUE TO EARLY VENTRICULAR FIBRILLATION IN MYOCARDIAL INFARCTION: VALUE OF REVASCULARIZATION, AN EXPERIMENTAL STUDY

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To evaluate the role of myocardial revascularization (REVAS) in the management of cardiac arrest following acute infarction (INF), 76 conscious, intact dogs were studied. Acute INF was produced in the conscious state by inflating a previously implanted balloon cuff device around the left anterior descending artery. Primary ventricular fibrillation (VF) developed in 29% (22/76). Twelve of these 22 could not be resuscitated, the other 10 recovered to a fully conscious state with normal arterial pressures and normal arterial blood gases. In 2 dogs, no REVAS was carried out and in the other 8, REVAS was carried out within 5 hours of INF in conscious state by deflating the previously implanted balloon cuff. The values of heart rate, left ventricular (LV) systolic, end-diastolic and developed pressures, cardiac output, stroke volume, stroke work, peak dp/dt of LV pressure, ejection fraction, myocardial oxygen and lactate extraction in these 10 resuscitated animals were similar to those of the other 54 INF animals who did not have primary VF. Five of the 8 REVAS dogs died within 24 hours, 3 survived; 1 of the 2 non-REVAS animals died. The INF size of the survivors as well as non-survivors averaged .34 of LV mass and was similar to the average INF size of the other 54 dogs (.31 of LV mass).
It is concluded that myocardial REVAS even if carried out in the intact, awake state without anesthesia or thoracotomy, does not prevent early mortality in acute INF in animals who have been successfully resuscitated from VF, and INF size in these REVAS dogs is not reduced.

DOES CHRONIC RECURRENT RIGHT VENTRICULAR TACHYCARDIA CONSTITUTE A SYNDROME?

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Ventricular tachycardia originating in the right ventricle (RVT) is characterized by tachycardic QRS complexes of left bundle branch block pattern. Seven patients (pts) with chronic recurrent RVT have undergone full diagnostic evaluation at the University of Illinois Medical Center during the last four years. One of the pts, who had severe biventricular congestive cardiomyopathy, will not be further presented in this report. Of the remaining six pts, two were males and four were female, with ages ranging from 18 to 52 (mean 38 years). All six had palpitation, with two also having several syncopal episodes. Cardiac examination was within normal limits in all. Resting electrocardiogram revealed conducted beats having normal QRS morphology and normal QTc. Cardiac catheterization revealed normal right and left-sided pressures (with the exception of slight RVEDP elevation in 2 pts), normal cardiac index (2.4 - 6.8, mean 4 liters/m^2), and normal ejection fraction (61-77%, mean 67%). Left ventricular and coronary angiography revealed no abnormalities. One of the six was lost to follow-up. The remaining 5 have been followed for 3 to 84 months (mean follow-up 3½ years) from the time of initial diagnosis of RVT. All have been resistant to anti-arrhythmic drugs singly and in combination. Despite this, the five are currently alive and well. In conclusion, chronic recurrent RVT appears to constitute a syndrome of unknown etiology characterized by lack of other evidence of organic heart disease, onset at relatively young age, resistance to anti-arrhythmic therapy, and lack of progression to sudden death.

THE REPETITIVE EXTRASYSTOLE AS AN INDEX OF VENTRICULAR VULNERABILITY TO FIBRILLATION

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Current models for the study of ventricular vulnerability have employed ventricular fibrillation (VF) as their endpoint. The subsequent process of defibrillation, with its concomitant disruptive changes, precludes usage of such models in the conscious animal. The present study was undertaken to define the ventricular vulnerable period (VP) using an endpoint of repetitive ventricular extrasystoles (RE). In 20 chloralose-anesthetized dogs paced at a constant rate, the VP was scanned at 1 msec intervals and 2 ma increments with a transvenous bipolar right ventricular catheter. The points at which RE and VF occurred were determined. In 13 control dogs (31 determinations) RE occurred at 24 ± 2 ma and VF at 36 ± 2 ma; the RE/VF ratio being 67 ± 3%. In all determinations RE preceded VF. RE and VF occurred at precisely the same time in the cardiac cycle; RE at 124 ± 2 msec after the pacing impulse and VF at 124 ± 2 msec. Bilateral vagal stimulation in 7 dogs shifted ventricular vulnerability further into diastole and produced RE at 141 ± 7 msec and VF at 140 ± 6 msec with a RE/VF ratio of 79 ± 4%. Left stellate ganglion stimulation in 7 dogs shifted both RE and VF 10 msec earlier into diastole. The RE/VF ratio was 68 ± 6%. In conclusion, RE occurs in the cardiac cycle at precisely the same time as does VF, at a current approximately 33% less than VF. Alteration in sympathetic and parasympathetic tone produces but little change in the RE/VF relationship. These data support the view that the RE can be used as a reliable predictor of, and substitute for VF -- obviating defibrillation as a necessary condition for the study of ventricular vulnerability.

REDUCTION OF PULMONARY VENOUS PRESSURE (PVP) WITH PROPRANOLOL IN MITRAL STENOSIS DURING SINUS RHYTHM.

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In patients with mild or moderate pure mitral stenosis (MS) and sinus rhythm (NSR) symptoms are usually due to elevated pulmonary venous pressure (PVP) rather than to low cardiac output (CO) or right ventricular failure. For any given valve area, PVP is an inverse exponential function of heart rate (HR) and CO. Digitalis is seldom of value in such patients. Propranolol lowers both HR and CO and thus might be expected to lower PVP. Thus, HR, CO, pulmonary artery mean pressure (PAM), left ventricular end diastolic pressure (LVEDP) and PVP were measured in 7 patients with MS in NSR before and 10 minutes after 2 mg of I. V. Propranolol. After Propranolol the following parameters fell: HR by 13.7 beats/min. ± 3.0 ($P < .005$), CO by 800 cc/min. ±200 ($P < .01$), PAM by 8.0 mmHg±1.8 ($P < .005$), and PVP by 6.7 mmHg±1.6 ($P < .005$) from 25 to 18 mmHg. LVEDP did not change. No adverse effects or symptoms attributable to low cardiac output appeared. Thus Propranolol may benefit patients with MS in NSR whose symptoms are due to elevated PVP. It is probably contraindicated in patients with very low basal cardiac output or severe left ventricular dysfunction.

SEQUENTIAL ALTERATIONS OF LEFT VENTRICULAR COMPLIANCE FOLLOWING MYOCARDIAL INFARCTION: COMPARISON OF ACUTE, EARLY AND LATE RECOVERY PERIODS IN PATIENTS WITH SIMILAR PUMP DYSFUNCTION. Richard R. Miller, MD; James Price, MD; Ezra A. Amsterdam, MD, FACC; Dean T. Mason, MD, FACC, University of California at Davis, California.

Although clinical studies have indicated left ventricular (LV) compliance↓ acutely with myocardial infarction(MI), subsequent diminution of stiffness has only been implied. Thus 56 patients(pts) were designated into 3 groups according to time of cardiac catheterization following MI:I) acute(0-3 days, mean 1.9):II)early recovery(2-11 weeks, mean 4.8), and III)late recovery(16 weeks). Importantly, the 3 groups were matched for similar LV dysfunction by ratio of stroke work index(SWI gm-m/M^2)/LV end-diastolic pressure(EDP mmHg). The passive elastic modulus($\underline{a}$) index of LV compliance was calculated in which $\underline{a}$ is the derived slope constant obtained from $\Delta P/\Delta V$ and $\bar{P}$: ΔP=LV diastolic pressure change; ΔV=stroke index and $\bar{P}$=mean LV diastolic pressure. (In normal pts $\underline{a}$ is 0.009; $\underline{a}$↑ indicates reduced compliance.) 13 Group I pts with acute MI, 6 anterior (AMI) and 7 inferior (IMI), had SWI/LVEDP 2.26 and $\underline{a}$=.043 with correlation coefficient(r)=.73. 18 Group II pts in early recovery stage, 7 AMI and 11 IMI, had SWI/LVEDP 2.40 and $\underline{a}$=.027(r=.70). 25 Group III chronic pts, 11 AMI and 14 IMI, had SWI/LVEDP 2.43 and $\underline{a}$=.031(r=.85). Greatest↓ LV compliance occurred acutely with MI; substantial improvement toward normal took place by 5 weeks without change thereafter. Reduced stiffness after first few days of acute MI shown in this study is related to spontaneous reduction of pulmonary congestion. Finally, despite scar formation LV does not become substantially less distensible after early recovery period; thus LV with old MI retains same degree of reduced compliance which provides a chronically operative compensatory mechanism aiding pump ejection.

CRITERIA FOR CORONARY ARTERIOGRAPHY
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The feasibility of using clinical descriptors targeted for survival to improve criteria for performing coronary arteriography was investigated in 945 consecutive patients (pts) with significant coronary artery disease (CAD). Fifty-seven clinical variables were analyzed by both a multiple logistic and categorical logical tree method to determine the most effective predictors of survival. Follow-up data were obtained at 6, 12, 24 and 36 months and were 99.5% complete. Survival rates were calculated by life table analysis. The most powerful four variables - age $<$ 50 vs $\geq$ 50 years and the presence or absence of previous myocardial infarction, congestive heart failure and cardiomegaly on chest film - interacted to classify all pts in terms of 16 possible subgroups. The 6 subgroups in which medical therapy resulted in at least 98% survival at 6 months were pooled to define a low risk (LR) group. The other 10 subgroups were joined to form a high risk (HR) group. The subsequent 12, 24 and 36-month survival of the 193 medically-treated (MT) pts in the LR group was significantly different from that of the 324 MT pts in the HR.group (95% vs 71% at 36 months, $p<.0001$). Within the LR group, the survival rate of the 193 MT pts was significantly better than that of the 185 surgically-treated pts at 6, 12, 24 and 36 months (95% vs 87% at 36 months, $p<.01$). These data indicate that CAD pts with a low risk of dying ($<2\%$) in 6 months can be identified without cardiac catheterization. This observation suggests that patients with low risk patterns should be treated medically for six months prior to determining the need for cardiac catheterization.

THE TRICUSPID VALVE IN CHILDREN - AN ECHOCARDIOGRAPHIC AND PHONOCARDIOGRAPHIC STUDY
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Evaluation of tricuspid valve closure was made by echocardiography and phonocardiography in 40 normal subjects (age range 3 days to 20 years). The intervals between the Q wave of the electrocardiogram and tricuspid closure (Tc) and between the Q and mitral closure (Mc) were measured, and the difference (Δ) between Tc and Mc determined. These values were then compared to patients with: 1) Ebstein's anomaly (10 patients); 2) Transposition of the great arteries (TGA - 15 patients); 3) Billowing posterior mitral leaflet syndrome (BPMLS - 12 patients); 4) Right bundle branch block (RBBB - 15 patients); 5) Atrial septal defect (ASD - 10 patients). In patients with Ebstein's anomaly, Δ was always large, and a value of greater than 70 msec was diagnostic of the condition. No other group had values in this range. In patients with partial or complete RBBB, Δ was within normal limits, and wide splitting of the first heart sound was not a diagnostic feature. Patients with BPMLS and secundum ASD had Δ values similar to normals. Most patients with TGA had Δ values that were negative, i.e., mitral valve closure occurred after tricuspid valve closure. This is contrary to the classic concept that Mc precedes Tc. Thus, echocardiographic determination of Δ values may provide a clearer understanding of hemodynamic factors which influence atrio-ventricular valve closure.

ABNORMALLY CONTRACTING SEGMENT SIZE FOLLOWING ANTERIOR AND INFERIOR MYOCARDIAL INFARCTION AND ITS RELATIONSHIP TO LEFT VENTRICULAR FUNCTION. Roger E. Moraski, MD; John A. Mantle, MD; William J. Rogers, MD; Charles E. Rackley, MD, FACC; Richard O. Russell, Jr., MD, FACC. University of Alabama Medical Center, Birmingham, Alabama.

Eighteen patients (pts) with anterior and 24 pts with inferior myocardial infarction were studied an average of 12 and 10 months, respectively, following their only myocardial infarction, to determine if the size of the resultant left ventricular (LV) abnormally contracting, akinetic or dyskinetic segment differed. The size of the abnormally contracting segment (ACS) was then related to LV function in each group of pts. A diagnosis of myocardial infarction required evolutionary ST-T wave changes, an abnormal rise and fall of SGOT and Q waves 0.04 sec in duration in at least two standard ECG leads. After measuring LV end-diastolic pressure (EDP), LV biplane angiograms (6 frames/sec) were done recording heart rate. From superimposed end-diastolic and end-systolic LV silhouettes, the percent (%) ACS was calculated as the ratio of length of ACS to total perimeter of the end-diastolic film. LV end-diastolic volume (EDV), ejection fraction (EF) and mass were measured. LV compliance was calculated as a linear approximation by the formula: Angiographic stroke volume/end-systolic volume/LVEDP-lowest early diastolic pressure.

The % ACS following anterior myocardial infarction was 19 ± 11% and following inferior myocardial infarction 12 ± 9%, $p<.05$. LVEDP was higher (16 ± 7 mmHg vs 10 ± 7 mmHg, $p<.005$) and EF lower (.33 ± .09 vs 41 ± 10, $p<.01$) following anterior myocardial infarction. Heart rate, LVEDV, mass and compliance did not differ significantly.

Thus, the size of the ACS following anterior myocardial infarction is greater than that following inferior infarction; the larger ACS is associated with more severe LV dysfunction as measured by LVEDP and EF.

INFLUENCE OF LEFT ATRIAL SIZE AND AGE ON THE DEVELOPMENT OF ATRIAL FIBRILLATION IN PATIENTS WITH MITRAL VALVE DISEASE AND ASYMMETRIC SEPTAL HYPERTROPHY

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Systemic embolization is a frequent and often devastating complication in patients (pts) with both mitral valve disease and asymmetric septal hypertrophy (ASH). Embolization usually occurs in pts in atrial fibrillation (AF), particularly those who recently converted from normal sinus rhythm (NSR) to AF. To define those factors associated with AF, 84 nonoperated pts with mitral valve disease and 129 nonoperated pts with ASH were studied by echocardiography. We found that both left atrial transverse dimension (LATD) and age are important determinants of atrial fibrillation. For example, none of the 58 pts <40 yrs of age with an LATD <45 mm was in AF. In contrast, 67 of 76 pts (88%) above age 40 yrs with an LATD $\geq$45 mm had AF. The frequency of AF was considerably lower in the subgroups of pts with a) age <40 yrs who had LATD $\geq$45 mm (28%) or b) age >40 yrs who had LATD <45 mm (7%). These data indicate that in two forms of structural heart disease of significantly different etiology, namely, mitral valve disease and ASH, AF occurs with high frequency only in pts age $\geq$40 yrs who have LATD $\geq$45 mm. Of particular relevance to the question of prophylactic anticoagulation, 17 pts in NSR at time of study had a history of paroxysmal AF. Of these 17 pts, 14 had an LATD $\geq$40 mm and were older than 40 yrs. Thus, it appears that pts in NSR who are likely to develop AF can be identified by age and LATD criteria, a finding that may be useful in decisions concerning prophylactic anticoagulation.

SODIUM INTAKE AND FUROSEMIDE ADMINISTRATION IN AZOTEMIC PATIENTS WITH SEVERE HYPERTENSION

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The clinical response of arterial blood pressure and renal clearances were evaluated in seven hypertensive azotemic patients to determine the optimal level of sodium intake and diuretic dosage. All patients were azotemic, severely hypertensive and receiving full doses of antihypertensive agents. The patients were hospitalized in a metabolic ward and were continued on their usual antihypertensive and diuretic medications for a three day control period. After the control period, the previous diuretic was discontinued and each of the patients received the following regimens for five days; Period I, 20 meq. sodium diet; Period II, 80 meq. sodium diet and furosemide 80 mg. daily; Period III, 200 meq. sodium diet and furosemide 160-240 mg. daily. With these regimens, the average clearances of creatinine, inulin and PAH remained unchanged, whereas the average arterial pressure was better controlled in the liberal sodium and high dose furosemide Period III. The average arterial pressure was 158/99 in the control period, 159/101 in Period I, 152/97 in Period II and 138/89 mm.Hg in Period III. It was concluded that in azotemic patients with severe hypertension who were receiving full doses of antihypertensive medications, liberal sodium intake with high doses of furosemide allowed for better control of arterial pressure without changes in renal function.

PROTECTION OF ISCHEMIC MYOCARDIUM IN MAN BY METHYLPREDNISOLONE

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The effect of the administration of pharmacologic doses of corticosteroids on the extent of acute myocardial infarction and upon subsequent mortality was assessed in 42 patients. After infarction size had been predicted from analysis of early (7 hour) serum creatine phosphokinase (CPK) changes with a curve fitting procedure based upon nonlinear Gauss-Newton stepwise iterations, each patient received 2 gm of methylprednisolone (MP). In 23 patients a second 2 gm dose of MP was administered either 6 or 12 hours after the initial dose. Completed infarction size (ISc) was calculated from all available CPK data (70-160 hours).

In 24 control patients with acute myocardial infarction there was a close correlation between predicted infarction size (ISp) and ISc (ISc = 0.97 ISp + 2.53, r = 0.97). In 42 treated patients ISc was significantly less than ISp (predicted = 104.7 $\pm$ 14.3 (mean $\pm$ S.E.) CPK-gram-equivalents (CPK-gm-eq), completed = 82.2 $\pm$ 8.7 CPK-gm-eq, $p < .01$, mean difference = 20%). In 29% (12/42) of those patients treated ISc fell below the 95% confidence limit of ISp. The exponential clearance of CPK (kd) was approximated in controls (kd = .00097 $\pm$ .0005 min^{-1}) and treated patients (kd = .00101 $\pm$ .0005 min^{-1}) and found to be similar. Mortality within 6 months after myocardial infarction in treated patients was less than 50% of that in controls matched for similar ISp ($p = .05$).

These data suggest that pharmacologic doses of methylprednisolone in certain patients with acute myocardial infarction result in apparent salvage of ischemic myocardium.

DOPAMINE IN THE TREATMENT OF LOW CARDIAC OUTPUT STATE. COMPARISON WITH ISOPROTERENOL AND L-NOREPINEPHRINE

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Twenty-two patients were studied in low cardiac output state following open heart surgery (mitral -, aortic valve -, congenital heart disease). DOPAMINE (DOPA) increased cardiac index (CI) and heart rate (HR), it decreased systemic vascular resistance (SVR), but less than ISOPROTERENOL (ISO). DOPA increased systolic and mean arterial pressures (MAP), but less than L-NOREPINEPHRINE (L-NE). Both, DOPA and L-NE increased myocardial O_2 consumption (MV_{O2}, ml/100g/min) by increasing coronary blood flow (CBF). Myocardial O_2 extraction (Ex_{O2},%) remained unchanged, indicating that increase in CBF was mediated by myocardial O_2 requirements. ISO increased CBF and MV_{O2} by far more. Myocardial Ex_{O2} decreased, indicating that rise in CBF was mediated by primary vasodilation. Myocardial lactate utilization (MV_L, μM/100g/min) remained normal with all 3 catecholamines. - DOPA increased urine output (ml/hr) unproportionately more than ISO, compared to the same increments in increases of CI. The table shows absolute changes in mean values:

	HR	CI	MAP	CBF	MV_{O2}	Ex_{O2}	MV_L	Urine
DOPA	+19	+1.11	+ 7	+23	+2.84	+3	-1.8	+75
L-NE	+ 9	+0.20	+23	+13	+1.64	+2	-8.2	- 8
ISO	+28	+0.95	- 7	+63	+4.05	-6	+8.6	+28

CONCLUSION: DOPA is the preferable inotropic agent in non-coronary shock. In contrast to ISO it is less oxygen costly to the myocardium, not a primary coronary vasodilator and maintains MAP. DOPA may be beneficial in the temporary treatment of coronary shock. In contrast to L-NE it improves peripheral perfusion. It exerts, however, a stronger beta adrenergic effect, which is potentially harmful for ischemic tissue.

MYOCARDIAL PROTECTION DURING AORTIC VALVE REPLACEMENT. Donald Mulder, M.D., FACC, Gordon Olinger, M.D., James V. Maloney, M.D., Douglas McConnell, M.D. and Gerald Buckberg, M.D. UCLA Medical Center, L.A., Calif.

Depressed cardiac performance (requiring inotropic support) following aortic valve replacement (AVR) is usually due to ischemic subendocardial necrosis resulting from inadequate myocardial preservation. Results following AVR in 40 consecutive patients reported previously (Group I) with the heart protected by topical hypothermia during ischemic arrest (12), or ventricular fibrillation with coronary perfusion (28), are compared with 40 consecutive recent patients (Group II), where the heart was maintained in a beating, non-working state in 39 patients, but fibrillated in one. Inotropic support was required in 33% of Group I patients (ischemic arrest 4/12, ventricular fibrillation 9/28). In Group II only the fibrillated patient (3%) required inotropic support; none was required in the remaining 39 patients with a beating, non-working heart. In Group I the 3 deaths (8%) were related to subendocardial injury (intractable cardiac failure or arrhythmia), while the 2 deaths (5%) in Group II were due to sepsis or hemorrhage. In addition data will be presented including simultaneous aortic, left atrial, left ventricular pressures and intracavitary EKG which support the concept that marginal coronary perfusion, although adequate to sustain the heart in a beating state, will result in demonstrable subendocardial ischemia not detectable by conventional EKG. We conclude that myocardial protection is most adequate when the heart is maintained in a beating, non-working state by perfusing the coronaries continuously at such a flow rate and perfusion tip pressure that the intracavitary EKG shows no evidence of subendocardial ischemia. This method of preservation avoids the most common cause of depressed cardiac performance following AVR.

USE OF PRECORDIAL R WAVE MAPPING TO DETECT CHANGES IN MYOCARDIAL ISCHEMIC INJURY. James E. Muller, MD; Peter R. Maroko, MD, FACC; Eugene Braunwald, MD, FACC. Depts Med, Harvard Med Sch & Peter B Brigham Hosp, Boston, MA.

The present study was undertaken to determine whether changes in the loss of precordial R wave voltage can be used to detect changes in ischemic damage following coronary artery occlusion. In 14 dogs 30 epicardial and 30 precordial electrocardiographic leads were recorded. In 7 control dogs a branch of the left anterior descending coronary artery (LAD) was ligated permanently. In 7 experimental dogs 2 branches of the LAD were initially occluded; 15 minutes later a zone of myocardium was reperfused by release of one of the occlusions. Twenty-four hours later the 26 myocardial biopsies taken from sites in the nonreperfused areas with ST segment elevation 15 min after occlusion showed markedly depressed creatine phosphokinase (CPK) activity (12.8±0.7 IU/mg protein) and abnormal histology while the 15 sites in the reperfused zones showed normal CPK activity (30.8± 1.2 IU/mg protein) and normal histology. Epicardial R waves of the nonreperfused sites fell 31.0±7.9% (from 15.8mV) 15 to 60 min post occlusion while R waves of the reperfused sites did not change during the same period. The mean precordial R wave voltage of sites exceeding 0.2mV of ST elevation 15 min following occlusion fell significantly more ($p<0.05$) (from 1.14±0.15 to 0.75±0.06 mV) in the control group than in the reperfused group (from 1.06±0.09 to 0.96±0.17mV) during the ensuing 45 min. Thus precordial R wave mapping of sites with ST segment elevation may be useful in detecting protection of myocardium jeopardized by ischemia.

EFFECT OF ATRIAL FIBRILLATION ON RIGHT VENTRICULAR FUNCTION IN PULMONARY HYPERTENSION

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Right ventricular (RV) function and tricuspid regurgitation (TR) determine cardiac output (CO) in acute pulmonary hypertension. The importance of the loss of right atrial (RA) function with atrial fibrillation (AF) has not been defined. Biplane cineangiographic right ventricular volumes (RVV) were obtained in 8 closed-chest dogs in sinus rhythm (NSR) and in atrial fibrillation at similar ventricular rates (HR) during balloon catheter-induced progressive pulmonary artery (PA) hypertension. Forward RV stroke volumes (RVFSV) were measured by indicator-dilution while total stroke volumes (RVTSV) were calculated from the RVV: the difference between RVTSV and RVFSV represented TR. Deterioration in right heart function with AF occurred at all levels of mean PA pressures 10-50 mm Hg. The change from NSR to AF at a mean PA pressure of 50 mm Hg resulted in a significant decrease in RVTSV (-30%), RVFSV (-26%), RV end-diastolic volume (-10%) and EF (-23%) while RV end-systolic volume, TR, HR, and aortic pressure did not change. Thus, the change from NSR to AF deteriorates cardiac function in acute pulmonary hypertension due to loss of right atrial function.

PREDICTION OF CARDIAC MORTALITY IN UNOPERATED PATIENTS WITH ATHEROSCLEROTIC HEART DISEASE

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The seven most important predictive factors were selected from 339 variables derived from clinical examination, maximal exercise stress testing, and cardiac angiography in 476 patients who underwent coronary arteriography but not surgical therapy during a 15 month period. In that time 42 died of cardiac causes. The results of stepwise multivariate analysis to derive an equation, risk index = constant + $a_1 x_1 \ldots + a_n x_n$ are shown: Constant = 1099

Factor	Coefficient	Std Error	F	R^2
EF	-2.35	1.33	3.1	.12
CA Index	0.25	.15	2.8	.15
EDV (cc/m^2)	1.87	.78	5.8	.17
ΔHR	-1.86	.80	5.3	.18
History of CHF	1.14	.56	4.1	.19
FAI	-1.13	.82	1.9	.20
Stenosis RCA	.70	.62	1.3	.21

(EF = Ejection Fraction, CA Index = Coronary Artery Disease Index, EDV = End-Diastolic Volume, ΔHR = Change in Heart Rate with Exercise, FAI = Functional Aerobic Impairment, Stenosis RCA = % Stenosis Distal 1/3 Right Coronary Artery). Examined singly, ejection fraction is the most important determinant of early cardiac death. The addition of angiographic variables improves prediction to 21% while it was only 8% after clinical examination and 11% if exercise results were also used. In 280 patients where risk index was calculated there was a highly significant difference between the values for living and dead patients ($P<.0002$). The mortality rate was 3/158 for those with indices less than the mean and 1 standard deviation while it was 5/31 (16%) in those with higher indices.

ECHOCARDIOGRAPHIC FEATURES OF THE INTRA-ATRIAL BAFFLE IN D-TRANSPOSITION OF THE GREAT VESSELS

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Eleven patients with dextro-transposition of the great vessels (age 8 months to 4 years), were studied by echocardiography following Mustard's procedure. Eight of them were also studied preoperatively. Postoperatively all patients demonstrated abnormal echoes in the atrial cavity behind the pulmonary root. In nine, the motion pattern generally resembled that produced by a stenosed atrio-ventricular valve with a sharp anterior movement followed by flattening in diastole and rapid posterior excursion in systole. The maximum amplitude of motion ranged from 4 to 9 mm (average 6.6 mm). In the remaining two cases, the anterior diastolic movement was attenuated. Similar abnormal echoes with larger amplitudes of motion (10-14 mm) were observed in the vicinity of the tricuspid valve in 3 patients while poorly moving, multiple or thick conglomerate echoes (2-11 mm wide) were detected in the remainder. Echocardiographic contrast studies performed by injecting indocyanine green via catheters placed on either side of the intra-atrial baffle identified it as the source of the abnormal echoes. Following surgery, coarse diastolic undulations of the mitral valve (10 cases) and the tricuspid valve (4 cases) were noted. Also, fine flutter of both atrio-ventricular valves, not present before, appeared after operation in 2 patients. These findings may be related to the abnormal blood flow in the atria resulting from the presence of the baffle. Echocardiography appears useful in delineating the character and movement pattern of the intra-atrial baffle and this may have potential in evaluating its long-term functional status.

VENTRICULAR ECHOES WITHOUT ATRIAL PARTICIPATION

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Data in five patients (66-82 yrs.) who exhibited ventricular echoes (VE) are presented. P-R interval was normal in 4 and slightly prolonged (220 msec) in 1 due to mild A-H delay (130 msec). In 2 patients regular ventricular pacing (VP)$\geq$100/min showed single VE without atrial participation at R-R intervals of 400-450 msec. In VE beats, the QRS complex was identical to the control normal sinus beats. Retrograde conduction to the A-V node was present in both but was absent to the atrium in 1 case. In 2 other patients single premature atrial beats (PAB's), at appropriate coupling intervals (A-A=360-470 msec) resulted in single VE without atrial participation. VE beat was identical to the control QRS complexes. The subsequent sinus P wave in the return cycle was blocked proximal to the His Bundle deflection. In the fifth patient regular atrial pacing (AP) at a cycle length (CL) ranging from 770-470 msec, resulted in VE and a quadrigeminal rhythm. A-H (145 msec) intervals remained constant in the beats preceding the echo beats. VE beat was not preceded by a P wave but resulted in block of the subsequent P wave. VE beats showed an H-V time similar to that of the control. These data: 1) demonstrate that the echo phenomenon was localized distal to the atria and proximal to the His Bundle, i.e., in the A-V node; 2) document that atrium is not an essential link for the occurrence of VE. In such cases the possibility of dual A-V nodal pathways may be entertained.

TREADMILL EXERCISE TESTING IN THE PRESENCE OF NONSPECIFIC ST-T CHANGES OR DIGITALIS EFFECT: CORRELATION WITH CORONARY ANGIOGRAPHY

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Investigation of the treadmill exercise test (TET) in patients (pts) with nonspecific ST-T changes or digitalis effect in the resting EKG was done in 93 pts with chest pain. Results of TET were correlated with findings of coronary angiography (CA). A positive (pos) TET was defined as horizontal or down-sloping ST segment depression of 1.0 mm or more in excess of the resting EKG. Of the 40 pts with no or insignificant coronary artery disease (CAD), 15 had taken digitalis, 26.7% (4/15) of whom demonstrated a pos response on the TET. Among the remaining 25 pts not receiving digitalis with normal coronary arteries, 4% (1/25) had a pos response. Of the 53 pts with CAD, 21 had taken digitalis, 71.4% (15/21) of whom had a pos response. Of the remaining 32 not on digitalis, 62.5% (20/32) had a pos response. The specificity of the TET was 95% for pts with CAD with resting nonspecific ST-T changes who were not on digitalis; the specificity of the TET for pts with CAD who had received digitalis was 79%. Sensitivity rates were 63% and 71% respectively. By utilizing more stringent criteria in the interpretation of the TET results (greater than 1½ mm ST depression) of the pts on digitalis, only 6.7% (1/15) with normal coronary arteries and 47.6% (10/21) with CAD had a pos response. When the criteria for a pos response of the TET in pts receiving digitalis is 1½ mm or greater below the baseline EKG, the test is specific in 93.7% of pts and is usually indicative of CAD.

DISCRETE SUBVALVAR AORTIC STENOSIS IN CHILDHOOD

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Fifty children were seen with discrete subvalvar aortic stenosis (DSAS) from 1951-1974. The purpose of this study is to emphasize the occult nature of DSAS in the presence of associated cardiac defects. Ages ranged from 18 days to 14 years (median 3 years) when first seen. The obstruction was a fibrous diaphragm in 40 patients, a thicker collar-like fibromuscular diaphragm in 5 patients, a fibromuscular tunnel in 3 patients, and was not clearly delineated in 2 children with mild obstruction. Surgical resection is generally required, as the obstruction is usually severe and can be progressive. Thirty-seven children underwent at least one surgical resection of the DSAS. The left ventricular-aortic peak systolic gradients ranged from 20-160 mm Hg, with a median of 90 mm Hg. Twenty-eight children had significant additional cardiac defects, and in many the clinical, hemodynamic and angiographic signs of DSAS were obscured by the presence of the other defects. Fourteen patients had large left to right shunts: 9 ventricular septal defects (VSD), 4 patent ductus arteriosus (PDA), and 1 aortic-pulmonary (AP) window. In 4 patients with VSD, the DSAS was not detected by catheterization until after VSD closure or pulmonary artery banding. In 3 children with PDA and one with AP window, the DSAS was not evident clinically until the shunts were closed. DSAS was masked in 4 of 7 children who had associated severe valvar aortic stenosis or coarctation, and in 2 of 5 patients who had severe associated muscular subaortic stenosis. A high index of suspicion and quality angiography are required to diagnose DSAS in patients with significant associated cardiac defects.

INTERRELATIONSHIPS BETWEEN BLOOD PRESSURE AND CONTRACTILE STATE IN ACUTE UREMIA

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Blood pressure (Bp) and left ventricular contractility are increased in rats 24 hours after bilateral nephrectomy. To investigate the role systemic hypertension plays in the increased contractile state, the left ventricle was studied in open chest rats during both ejection (E) and isovolumic contractions (ISO) 24 hours after sham surgery (S) or bilateral nephrectomy (U)(BUN 130). Left ventricular systolic pressure (LVP) and max dP/dt were higher in U than in S during both E and ISO. The differences between U and S were not diminished by IV propranolol. When the Bp course was kept normal in U throughout the 24 hours with IP phenoxybenzamine, dP/dt was 47% higher during E and 57% higher during ISO in U than in S. When S were treated 24 hours with SC methoxamine to equal the Bp course of U, indices of contractility increased toward those of U, but the rise in dP/dt from E to ISO in U was twice as high as in S. With milder U (5/6 nephrectomy) studied at 48 hours (BUN 48), there was no hypertension but LVP and dP/dt during ISO were 24 and 29% greater than S. All differences are $p < 0.05$. In all conditions studied EDP was the same or lower in U hearts than in paired S, but max dP/dt/max P was higher in U than S. These data indicate that although early hypertension can be associated with augmented contractility, the increase in intrinsic contractility seen early in the uremic state can be dissociated from hypertension and from B-adrenergic influences. Therefore, acute uremia per se appears to cause increased contractility.

THE DIAGNOSIS AND SURGICAL TREATMENT OF COR TRIATRIATUM

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Of the cardiac defects causing obstruction of the pulmonary venous return, cor triatriatum is one of the more unusual. From 1961 through 1974, 11 patients (pts.) were treated for this congenital anomaly. The age ranged from 7 months to 36 years with two pts. under the age of one year and eight pts. under the age of six years. There were eight females and three males. Presenting symptoms were congestive heart failure and frequent respiratory infections. Chest X-ray showed cardiomegaly and increased vascular markings in all pts. The electrocardiogram demonstrated right atrial and ventricular hypertrophy. Cardiac catheterization was done on all patients and preoperative diagnosis was obtained in only seven of the 11 pts. In five pts. the diaphragm dividing the left atrium into two chambers was seen angiographically and in three pts. a gradient across the diaphragm was demonstrated. All pts. had pulmonary arterial hypertension. Associated anomalies were present in eight of the 11 pts. Four had associated atrial septal defects and two endocardial cushion defects. Associated anomalies were repaired at the same time of excision of the cor triatriatum membrane. Operation consisted of either right or left atriotomy and total excision of the membrane. There was one operative death which occurred six days following surgery. All pts. have shown vast improvement following surgery and there have been no late deaths. Early and late results were related to the amount of pulmonary vascular resistance present preoperatively. With present techniques, cor triatriatum can be easily diagnosed and results from surgical correction are gratifying.

CARDIOVASCULAR EFFECTS OF THE NEW ANTIARRHYTHMIC AGENT, VERAPAMIL

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Verapamil (V), an antianginal agent with potent clinical antiarrhythmic effects, was studied to investigate its cardiovascular properties. Microelectrode studies were performed in Purkinje fiber (PF) utilizing standard techniques. Resting potential amplitude, APD, and dV/dt were significantly depressed after exposure to $\geq 1 \times 10^{-6}$ M; effects on ERP were minimal. Conduction velocity in linear PF was depressed but only at $\geq 1 \times 10^{-5}$M. A marked negative chronotropic effect was noted in isolated sinus node with sinus arrest at $\geq 1 \times 10^{-5}$M. However, depression of PF automaticity was seen only at 1×10^{-4}M, suggesting V has more effect on the slow inward sodium current. This is supported by V's lack of effect on membrane responsiveness until exposure to 1×10^{-4}M. AV conduction studies performed in conscious dogs caused no significant changes in AH, HV, QRS intervals or heart rate at doses of 0.05, 0.1 and 0.2 mg/Kg IV; at a dose of 0.4 mg/Kg marked sinus suppression ensued. In dogs with chronic AV block, V caused an increase in ventricular automaticity. In anesthetized dogs, a dose of 0.05 mg/Kg resulted in a decrease in coronary flow (29.3 to 22.3 ml/min) possibly resulting from a decrease in LV dp/dt, aortic systolic pressure and heart rate. Doses $\geq$ 0.1 mg/Kg Iv produced similar but more pronounced changes interpreted as diminishing LV performance. In conclusion, the above studies demonstrate that V has a marked effect on sinus node function, lesser effects on PF and, in higher doses, may depress left ventricular function.

EFFECTS OF SUB-THERAPEUTIC TO THERAPEUTIC DOSES OF PROCAINE AMIDE ON THE ELECTROPHYSIOLOGICAL PROPERTIES OF THE ATRIOVENTRICULAR CONDUCTING SYSTEM IN MAN

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The effects of single intravenous infusions of low to relatively high doses (50 to 400 mg) of procaine amide (PA) on the functional properties of the atrioventricular (AV) conducting system were studied and correlated with plasma concentrations (PC) using His bundle electrograms and the atrial extrastimulus (A_2) method at constant cycle lengths (A_1A_1). Measurements were made within 5-10 minutes after PA dosing. 50 mg of PA (5 pts) resulted in PC <0.1 mg/L and produced no electrophysiological changes. 100 mg (PC 1.4 mg/L) did not change His-Purkinje system (HPS) conduction (HV interval) but increased HPS refractoriness in 3 of 5 pts. 200 mg (9 pts), 300 mg (6 pts), 400 mg (6 pts) resulted in progressive increases in PC (2.32, 3,83, 4.23 mg/L respectively) which paralleled progressive increases in HV interval (5, 8, 9 msec respectively) and refractoriness (8, 16, 26 msec respectively). In some pts the effect of 100-200 mg on HPS refractoriness was subtle and could only be detected by plotting H_1H_2 and V_1V_2 against the full range of A_1A_2. Increases in atrial refractoriness were observed at doses of 300 mg or >. Doses of 100-300 mg decreased AV nodal refractoriness whereas 400 mg produced an increase. Premature ventricular beats with fixed coupling intervals were abolished with doses as low as 100 mg. The electrophysiological effects of PA correlate well with dose and plasma concentration. Cessation of some types of ventricular arrhythmia by sub-therapeutic doses of PA could be explained by the subtle changes in refractoriness within the HPS.

ROLE OF DIGITOXIN METABOLITES IN THE ENTEROHEPATIC CIRCULATION OF DIGITOXIN

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Conversion of water soluble biliary digitoxin metabolites in the gut back to digitoxin has been proposed as a mechanism to explain the prolonged biological half-life of digitoxin. To help clarify the role of digitoxin metabolites in the enterohepatic circulation, one group of dogs (donor dogs) was given H^3 digitoxin with 1 mg non-radioactive digitoxin intravenously. Bile was collected, extracted 4 times with 10 volumes of chloroform, and the water layer chromatographed (Gelman, SG paper) in two solvent systems to assure complete removal of digitoxin from bile. The digitoxin free bile, containing water soluble metabolites of digitoxin ($3.8-8.3 \times 10^8$ DPM) was then given intraduodenally to 4 other dogs (recipient dogs), with frequent collection of portal venous (PV), systemic venous (SV) blood, urine and bile. All samples were counted for radioactivity and DPM determined by internal standardization. Radioactivity appeared within 15 minutes in PV and SV blood. Urinary and biliary excretion occurred later, but reached very high values. Chloroform extraction and chromatography showed that no detectable digitoxin or other chloroform soluble metabolites were present in PV, SV blood, urine or bile. It is concluded that water soluble metabolites of digitoxin participate in the enterohepatic circulation, are not transformed back to digitoxin, and are themselves reabsorbed.

DETERMINANTS OF VENTRICULAR SEPTAL MOTION

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Echocardiographic studies of ventricular septal (VS) motion were performed in patients (pts) with a variety of cardiac disorders to define the determinants of septal motion. In 43 pts with right ventricular volume overload (RVVO) secondary to atrial septal defect, septal motion was frankly paradoxic in 35 (82%), flat in 4 (9%), and normal in 4 (9%). Pattern of septal motion was determined by the position of the VS relative to total cardiac diameter (distance from RV epicardium to left ventricular (LV) epicardium at end-diastole). All pts with normal septal motion, and no pts with flat or paradoxic motion, had a septal position (defined as the distance from RV epicardium to mid-septum/total cardiac diameter) at end-diastole $<.41$. When septal motion was measured (diastolic minus systolic septal position), the direction and magnitude of VS motion was linearly related to end-diastolic septal position ($r=.80$, $p<.01$). Septal motion correlated poorly with size of shunt ($r=.13$) and RV pressure ($r=.18$). A similar relation between septal position and septal motion was evident in 1) 14 pts with other causes of RVVO ($r=.82$), 2) 19 pts with LV volume overload ($r=.74$), 3) 10 pts with RV pressure overload ($r=.93$), 4) 10 pts with LV pressure overload ($r=.80$), and 5) 28 normal subjects ($r=.82$). We conclude that the direction and magnitude of septal motion is determined by septal position relative to total cardiac transverse dimension. Thus, although paradoxic septal motion is usually seen in conditions causing RVVO, it is not diagnostic of any particular hemodynamic burden. Rather, it is dependent upon the geometric position of the septum within the heart.

THE PROPRANOLOL WITHDRAWAL REBOUND PHENOMENON: ACUTE AND CATASTROPHIC EXACERBATION OF SYMPTOMS AND DEATH FOLLOWING THE ABRUPT CESSATION OF LARGE DOSES OF PROPRANOLOL IN CORONARY ARTERY DISEASE.

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It has been suggested that the sudden withdrawal of chronically administered high doses of propranolol (P) may be hazardous. To further clarify this clinical impression 20 patients (pts) with coronary artery disease (CAD) and severe angina pectoris receiving P 160-320 mg/day for 6-8 consecutive weeks in a double blind efficacy trial were evaluated for adverse effects upon abrupt changeover to placebo. Prior to withdrawal, no pts had increases in anginal attacks or nitroglycerin usage and there were no hospitalizations or deaths during the 6-8 weeks of P. However, within 2 weeks of discontinuing P, 12 pts (60%) had increases in angina from 7 to 11 attacks per week ($p<.05$) and use of nitroglycerin increased from 14 to 19 tablets per week ($p<.05$). Further, 3 pts developed unstable angina and were hospitalized. In addition, 1 pt was hospitalized with ventricular tachycardia, one pt had a massive myocardial infarction and died, and one pt had sudden death. Thus, not only did the frequency and severity of angina increase in the majority of pts when P was suddenly discontinued, serious exacerbations leading to hospitalization resulted in 6 pts (30%) and catastrophic complications resulting in death occurred in 2 pts (10%). Although the precise mechanism of the adverse rebound phenomenon remains speculative, this experience strongly suggests that propranolol chronically administered to pts with severe CAD should be reduced gradually rather than abruptly discontinued.

SEGMENTAL MYOCARDIAL STIFFNESS AS A DETERMINANT OF DYSKINESIS IN THE ACUTELY ISCHEMIC LEFT VENTRICLE.

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Previous studies from this laboratory have shown that, following experimental coronary occlusion, aneurysmal systolic bulging (dyskinesis) develops acutely, then gradually recedes. This might be due to progressive stiffening of the ischemic segment. To study this possibility, we instrumented eight dogs with epicardial segment length (SL) gauges attached to the surface of the left ventricle (LV) in the distribution of the nutrient coronary vessel to be occluded. The degree of dyskinesis was measured in muscle lengths (ML), where ML=peak amplitude of SL/end-diastolic SL. Segmental myocardial stiffness (K) was determined from simultaneous end-diastolic SL (EDSL) and pressure (LVEDP) measurements made during loading of the LV induced by transient aortic occlusion, where K=LVEDP in mmHg/% ΔEDSL. Results were (mean±SEM):

	Time after coronary occlusion			
	15 min	1 hr	3 hr	6 hr
ML	0.19±0.02	0.17±0.02	0.15±0.02	0.13±0.01
K	1.11±0.18	1.15±0.18	1.20±0.16	1.50±0.17

An inverse correlation was obtained between ML and K where $r=-0.66$ ($p<0.001$, $n=85$) and $ML=0.26-0.073K$. The studies indicate that paradoxical systolic expansion, which decreases with passage of time after onset of ischemia, may be explained by a gradual increase in segmental myocardial stiffness.

INTERACTION OF CALCIUM AND ISOPROTERENOL ON THE VENTRICULAR ACTION POTENTIAL IN DEPOLARIZED GUINEA PIG MYOCARDIUM

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Action potentials in myocardium depolarized to potentials less negative than ca.-55mV depend on the membrane current flowing through the slow channel. This current is augmented both by Ca++ and isoproterenol (ISP). We studied interaction of Ca++ and ISP in 79 guinea pig papillary muscles bathed in Tyrode solution containing 30 mM KCL at 4 different Ca++ concentrations: 1.8; 3.6; 6.0; and 8.0 mM/L. Resting membrane potential was -47 ± 4 mV. Without ISP, the maximum rate or rise (dV/dt) and the overshoot (OS) of the AP increased progressively with increasing Ca++ concentrations. Thus, at Ca++ 1.8 mM/L, dV/dt was 6.7 ± 3.4 V/sec and OS 19 ± 8 mV; at Ca++ 8.0 mM/L, dV/dt was 26.6 ± 7.4 V/sec and OS 37 ± 6 mV. With ISP (10^{-6}M/L) dV/dt increased by 152% at 1.8 mM/L Ca++ but the increase was less at higher Ca++ concentrations, and at 8.0 mM/L Ca++ dV/dt did not increase; OS increased at 1.8 mM/L Ca++ but did not change or decreased at higher Ca++ concentrations. Within ca.15 minutes, ISP superfusion caused progressive deterioration of AP and increase in stimulation threshold. The ISP-induced loss of excitability occurred within av.90 minutes at Ca++ 1.8 mM/L and within av.24 minutes at Ca++ 8.0 mM/L. ISP effects were reversible at lower but not at higher Ca++ concentrations. Our results show that both the early stimulating and the late depressing effect of ISP depend on Ca++ concentration. Increase in Ca++ concentration attenuates the stimulating effect of ISP on slow channel-dependent depolarization, and accelerates the deletorious effect of ISP on AP and excitability. These observations may be pertinent to therapeutic ISP application in the presence of depolarized (ischemic) myocardium.

FREE FATTY ACID SUPPRESSION WITH GLUCOSE-INSULIN-POTASSIUM IN PATIENTS WITH UNSTABLE ANGINA.

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Eighteen patients (pts) admitted to the Myocardial Infarction Research Unit with prolonged angina and ST-T changes were infused for 48 hours with glucose-insulin-potassium (GIK) to assess the clinical response and free fatty acid (FFA) suppression. The infusion (300 grams glucose, 50 units regular insulin and 80 mEq potassium/L at 100 cc/hour) was through the right atrial outlet of a Swan-Ganz thermodilution catheter and was begun within 12 hours of the onset of pain. Enzymes (SGOT, CPK, LDH) were measured every 8 hours, and FFA and blood sugar every 4 hours during the infusion. Right atrial pressure, pulmonary artery end-diastolic pressure (PAEDP) and cardiac output were serially monitored. During the infusion, only 4 pts had chest pain, none developed Q waves in the electrocardiogram, and none demonstrated a characteristic enzyme rise of acute myocardial infarction. Two patients died; one with recurrent ventricular tachycardia while receiving GIK and the other pt following coronary bypass surgery performed 10 days later. The mean FFA concentration of all 18 pts was 874 μEq/L prior to GIK infusion, 200 μEq/L during the infusion and 340 μEq/L 8 hours after the GIK was stopped. Hemodynamically, the pts either maintained normal values or showed improvement with a decrease in their PAEDP. These data suggest that pts with angina and acute ST-T changes can safely be instrumented for GIK infusion and that FFA can be suppressed to within normal limits. The suppression of FFA in this setting may be important for myocardial protection.

EFFECT OF VERAPAMIL ON ^{42}K TRANSPORT IN CANINE CARDIAC PURKINJE FIBERS

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Verapamil has been used clinically to promote coronary vasodilatation and to convert cardiac dysrhythmias. Both microelectrode and voltage clamp studies have shown that it suppresses inward Ca^{++} current in cardiac tissue and smooth muscle. Recent studies on cardiac tissue have shown verapamil to inhibit Na^{+} movement as well. In 6 experiments using isolated, perfused canine cardiac Purkinje fibers, we found that verapamil (0.5 mg/l) caused a mean decrease of relative uptake of ^{42}K by the fiber of 14.6% [a mean decrease of 20% in quiescent fibers and 13% in driven fibers (42/min)]. In 5 other Purkinje preparations, we measured 4 efflux periods (2 control, 2 verapamil) for each fiber and found a mean decrease in ^{42}K efflux of 29%. These data were significant at the 95% confidence level. Thus verapamil not only blocks transmembrane Ca^{++} and Na^{+} movements, but also inhibits transmembrane ^{42}K movements. Since this inhibition occurs in both driven and resting fibers, the K^{+} blockade is independent of changes in action potential size and configuration. Since verapamil is a large molecule and it is capable of reducing transmembrane movements of Ca^{++}, Na^{+}, and K^{+}, it is probably interacting nonspecifically with the membrane to cause a slowing of all transmembrane ionic movements, rather than interacting with and blocking specific channels for Ca^{++} as was originally postulated.

NON-INVASIVE ASSESSMENT OF VENTRICULAR RELAXATION AND FILLING.

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Isovolumic relaxation and ventricular filling have been studied with echocardiography (echo) in 55 patients (pts) and compared with cineangiograms (LV cine) in 15 of these pts. Echoes and LV cines were digitized on a computer to show continuous measurement of ventricular dimensions. Echoes showed mitral valve opening (MVO), and phonocardiograms showed aortic valve closure (A2) defining isovolumic relaxation (A2-MVO) in the absence of aortic regurgitation. A2-MVO was shorter in 8 pts with pure mitral regurgitation (MR) (5-60 msec, mean 25) than in 8 normal subjects (50-80 msec, mean 61, $p<0.001$). Shape changes prior to MVO were demonstrated as an increase in echo diameter before MVO in 47 of 55 pts; however, isovolumic shape changes were negligible in MR. LV cines showed corresponding isovolumic changes (increase of transverse diameter before increase in area of ventriculogram) in 10 of 13 patients, none with aortic regurgitation. During ventricular filling, the patterns of wall movement were similar on plots of echo dimension, transverse ventriculographic dimension, and ventriculographic area. Peak rates of change of wall movement measured by echo correlated with those measured by LV cine ($r=0.85$). Early rapid filling is often associated with a third sound (S3); however, no consistent relation was found between the timing of S3 and any feature of ventricular wall movement. These studies show: 1) isovolumic relaxation is brief in MR; 2) isovolumic shape changes are frequent and can be measured; 3)echo and LV cine give a similar reflection of ventricular filling; 4) factors other than ventricular filling may be involved in the etiology of the third sound.

SUDDEN DEATH AMONG POSTOPERATIVE PATIENTS WITH TETRALOGY OF FALLOT: A FOLLOW UP STUDY OF 251 PATIENTS FOR AN AVERAGE OF TWELVE YEARS.

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The long term prognosis of various types of conduction disturbances that occur in the postoperative patients with Tetralogy of Fallot(TF) is not well defined. A study was undertaken to evaluate this with special emphasis on sudden death. 251 patients who survived longer than one month postoperatively were included in the study. These patients were followed on an average of 12 years with a range of 6½ to 16 years. There were 25 patients(10%) with Right Bundle Branch and left anterior hemiblock - Bifascicular Block(BB) and 12 (4.8%) with Trifascicular Block(TB). 22% had normal electrocardiograms and 63.2% with Complete Right Bundle Branch Block(RBBB). Sudden death occurred in a total of 8 patients. 5 deaths were among those with RBBB. 4 of these had frequent premature ventricular contractions(PVC) for more than one month postoperatively. PVC occurred in 12 of the 159 patients with RBBB with sudden death occurring in 4(33%). 3 of the 12(25%) patients with TB died suddenly while no deaths occurred in BB alone. Progression of RBBB to BB occurred during a varying period of 1 month to 7 years. 56% of BB and 33% of TB developed during this period. Our study demonstrates that the occurrence of PVC with RBBB and TB are ominous signs in postoperative patients with TF. Prognosis of BB is good but the conduction disturbance can be of progressive nature. Long term careful follow-up is required for all patients with postoperative conduction disturbance.

IMPORTANCE OF ATRIAL CONTRACTION TO LEFT VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION.

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After myocardial infarction(MI)left ventricular(LV)end-diastolic pressure(EDP)is higher than mean pulmonary artery wedge pressure because of powerful atrial contraction (AC). To evaluate the significance of AC to LV function we studied 10 control(C)patients(pts)without cardiac disease and 17 pts 3 to 6 weeks after acute MI. Cardiac catheterization with simultaneous LV diastolic pressure(DP) and LV cineangiograms were obtained.

LV volumes and pressure were (mean ± SD):

	LV vol.(ml/M^2)			LVDP (mmHg)	
	Pre 'a'	EDV	LVSV	Pre 'a'	EDP
Controls	76±16	86±13	56±10	8±2	10±2
MI	91±36	107±38	46±19	13±6	21±11

EDV = end-diastolic volume; SV = stroke volume

Although LVSV was lower in MI than in C (46 vs. 56 ml/M^2), AC contributed more to LV filling and SV in MI than in controls (16 vs. 10 ml/M^2). Average AC to LVEDV was 11.9%(C), 15.4%(MI);to LVEDP was 20%(C),38.7%(MI); and to LVSV was 21.7%(C), 35.1%(MI). AC to LVSV and LV filling in MI pts was 31% in those with normal LVEDV and 35% in those with increased LVEDV.

In conclusion, in pts with MI, atrial contraction made a large contribution(35%) to LV stroke volume irrespective of the type of LV functional derangement that was present. Atrial contraction cannot be ignored and LVEDP should be used for assessment of LV performance.

CPK ISOENZYMES IN SUPRAVENTRICULAR TACHYARRHYTHMIAS

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Serum total creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (GOT) and lactate dehydrogenase (LDH) serial measurements and CPK isoenzymes, in 62 cases of transient supraventricular tachyarrhythmias, (mostly paroxysmal atrial fibrillation), without clinical or ECG evidence of acute myocardial infarction (AMI), were compared with data from 200 cases of AMI. AMI cases showed the usual pattern of enzymes elevation with an average total CPK of 98 units (range 25-330). (Normal total CPK values in our method: up to 20 units). The electrophoresis of CPK revealed a marked increase in MB CPK (myocardial fraction) up to 40%, besides the elevated MM fraction. From the 62 tachyarrhythmia cases, 28 showed a total CPK elevated to an average of 52 units (range 24-104) and 36 showed moderately elevated GOT. The increase in total CPK was due to the increase in MM isoenzyme (musculoskeletal fraction) with no MB present in 26 cases, but a minor increase in MB in only 2 patients (4-6%). The total CPK and the MM fraction remained elevated for only one day. A correlation between arrhythmia's duration or the heart rate and the increase in CPK was found. The elevation of only the MM fraction in most cases of arrhythmias suggests the mechanism of CPK elevation to be not myocardial necrosis, but, poor perfusion to the musculoskeletal apparatus.

Our data suggest, therefore, that a quantitative fractionation of the CPK isoenzymes can differentiate cardiac arrhythmias per se from myocardial infarction complicated by arrhythmia.

EFFECTS OF ALTERED PRELOAD ON V_{CF} AND OTHER LEFT VENTRICULAR EJECTION PHASE INDICES.

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Left ventricular (LV) mean circumferential fiber shortening rate (V_{cf}), ejection fraction (EF) and mean systolic ejection rate (MSER) are thought to reflect LV inotropic state. Although known to be affected by changes in LV afterload, their responsiveness to altered preload (Frank-Starling mechanism) is uncertain. This problem was assessed in ten normal subjects studied by non-invasive methods in the supine position and after 10 minutes of 75° head-up tilt. Echo LV diameter (D) and carotid pulse tracings were used to calculate LV end diastolic and stroke volumes (EDV and SV, by D^3 formula), ejection time (LVET), and V_{cf}, MSER, and EF. Systemic blood pressure(BP) was measured by sphygmomanometry, and heart rate (HR) counted from the ECG.

End diastolic LVD decreased with tilt(48±1.2 to 43±1.2 mm*) as did calculated EDV (115±8 to 82±7 ml*), and these data were interpreted as indicating a fall in LV preload. SV decreased (81±6 to 54±6 ml*), as did LVET (.31±.01 to .27±00 sec*), but there was no significant change in systolic or diastolic BP, or HR. V_{cf}, EF, and MSER were not significantly altered (1.09±.04 to 1.12±.05 circumferences /sec; .70±.02 to .65±.02; and 2.29±.07 to 2.43±.08 EDV/sec, respectively).

V_{cf}, MSER, and EF appear relatively unaffected by acute alterations in preload. That compensatory autonomic reflexes blunted potential changes cannot be excluded, although HR was not found to have increased.

*$p < .01$

QUANTITATIVE ECHOCARDIOGRAPHY: ACCURACY OF VENTRICULAR VOLUME ANALYSIS BY AREA-LENGTH, LINEAR REGRESSION AND QUADRATIC REGRESSION FORMULAE. Robert A. Ratshin, MD; Charles E. Rackley, MD, FACC; Richard O. Russell, Jr., MD, FACC. University of California, San Francisco Medical Center, San Francisco, CA.

Left ventricular volumes (LVVs) by quantitative echocardiography (QE) and quantitative angiocardiography (QA) were compared in 191 patients (pts) with myocardial and valvular heart disease. LVVs by QE were calculated using a cubed-function of the measured LV internal dimension (LV ID) derived from the area-length formula, and by linear and quadratic regression formulae derived from analysis of QE-measured LVID relative to the respective LVV by QA. LV Vs by QE have previously been calculated using a modification of the QA area-length formula with the assumption that the LV major:minor axis ratio is 2:1. The validity of this assumption has been questionned as a 2:1 major:minor axis ratio is rarely realized or stable throughout the cardiac cycle, in volume-overload compensated hearts or in hearts with regional abnormally contracting segments (ACS) of myocardium. The LVID by QE correlated with EDV by QA with r=0.942 and with ESV by QA with r=0.907 by linear regression and with r=0.965 and 0.963 respectively using quadratic regression. LV end-diastolic (EDV) and end-systolic (ESV) volumes by QE and QA correlated with r=0.957 (SEE ±33cc) and r=0.919 (SEE ±28cc) respectively using the area-length formula and omitting pts with ACS. LVEDV and ESV by QE and QA using linear regression formulae correlated with r=0.935 (SEE ±28cc) and 0.915 respectively, while using quadratic regression formulae correlation was with 0.968 (SEE ±22cc) and 0.965 (SEE ±21cc) respectively.

LVV analysis by QE using the quadratic regression formulae: $LVEDV = 359.8 - 151.3LVID + 21.0(LVID)^2$ and $LVESV = 119.6 - 74.7LVID + 15.7(LVID)^2$ appears to allow calculation of LVVs most accurately and with the lowest SEE.

THE EFFECT OF ATROPINE ON SINUS NODE FUNCTION IN ADULTS WITH SINUS BRADYCARDIA
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The diagnostic and therapeutic use of atropine in patients with sinus node dysfunction is controvertial. We therefore studied 15 patients with sinus bradycardia (SB) and determined atropine's effects on sinus node automaticity and sinoatrial conduction time (SACT). Atrial and His bundle electrograms were recorded during atrial premature stimulation (APS) and rapid atrial pacing at varying rates (60-150/min) before and after 1.0 mg of atropine IV. After atropine, mean sinus cycle length (SCL) shortened in 15/15 pts ($P<0.01$ in each, range 6-60%); mean SACT shortened in 15/15 pts (12/15 absolute shortening, 3/15 rate-related relative shortening). High atrial reentry during APS was abolished by atropine in 1/4 pts but was caused by atropine in 2/10 pts. After atropine, maximal sinus recovery time (maxSRT) decreased in 13/14 pts; maximal corrected SRT (maxSRT - SCL = maxCSRT) decreased in 11/14, was unchanged in 1/14, and lengthened slightly in 1/14. 1 of 14 pts showed a marked increase in maxSRT (2,632→10,920msec) and maxCSRT (1,153→9,867msec) after atropine despite shortening of SCL (1,479→953 msec) and SACT (93→83 msec). We conclude that atropine will significantly shorten SCL and SACT to some degree in virtually all patients with SB; but, because reentrant rhythms and adverse changes in SRT (and presumably in post-tachycardic suppression) may occur, we recommend electrophysiological testing in all patients with SB who are to be treated with atropine.

ABNORMAL INSPIRATORY DECREASE IN EJECTION TIME VERSUS PULSUS PARADOXUS IN PERICARDIAL EFFUSION
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The sensitivity and specificity of pulsus paradoxus (PP= inspiratory decrease of systolic arterial pressure > 15 mm Hg) and abnormal inspiratory decrease in ejection time (AIDET > 20 msec) in diagnosing tamponade physiology was investigated in 15 patients (pts) with pericardial effusion. Right heart, intra-arterial and intrapericardial pressures and ejection time from external carotid pulse tracing were obtained during spontaneous respiration. Tamponade physiology was diagnosed when right atrial and right ventricular diastolic pressures, which were elevated and equal to pericardial pressure, decreased with pericardiocentesis. Such physiology was present in 11 and absent in 4. None of the pts without tamponade had AIDET but 2 had PP. Among 11 pts with tamponade, 6 had PP, 7 had AIDET and 4 had both. The sensitivity and specificity of these two parameters was as follows:

(in percentage)	PP	AIDET	Both PP & AIDET	PP or AIDET
Sensitivity	55	64	36	63
Specificity	50	100	100	50
Overall Correctness	53	73	53	67

Higher sensitivity and specificity of AIDET when compared to intra-arterially measured PP was not statistically significant. Sensitivity is increased if diagnosis is made in the presence of one or the other parameter whereas specificity is increased in the presence of both.

SURGICAL CLOSURE OF PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS
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The ductus arteriosus often remains patent in premature infants, especially those with respiratory distress syndrome. If congestive heart failure develops, surgical closure may be necessary although it is reported to carry a high mortality.

Interruption of the PDA was carried out in 11 premature infants. Average gestational age was 30.7 weeks and birth weight was 1,325 kg. Operation was performed an average of six weeks after birth. Hypoxia, bradycardia, hypercapnia, and apneic episodes occurred frequently. All patients had a cardiac murmur suggestive of PDA and cardiac enlargement on electrocardiogram and chest roentgenogram.

Five critically ill infants were operated upon on the basis of clinical findings and in the six patients who underwent cardiac catheterization, aortic pressure averaged 66/36 mm.Hg. and pulmonary artery pressure was 37/14 mm.Hg. Average pulmonary flow was 20.9 L/min/m^2 and systemic flow 4.2 L/min/m^2, hence the ratio Q_p/Q_s was 5.5. Pulmonary resistance was always low, averaging 2.0 mm.Hg./L/min/m^2.

All patients except one required some degree of postoperative respiratory support. Nine (82%) were discharged home and continue to thrive. There were two deaths from progressive pulmonary insufficiency due to immaturity. Surgical closure of PDA in premature infants in congestive failure with respiratory insufficiency is essential for patients who have an otherwise poor prognosis.

IMPROVED QUANTIFICATION OF MYOCARDIAL INFARCTION BASED ON ANALYSIS OF SERUM CPK ISOENZYMES

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Prognosis after myocardial infarction correlates with infarct size estimated from serum CPK changes. However, noncardiac CPK may influence serum activity, particularly after i.m. injections, hypotension, or shock. Accordingly, we estimated infarct size from serial changes in serum MB CPK, an isoenzyme relatively specific to myocardium. MB CPK was assayed quantitatively with a fluorimetric procedure recently developed. Infarct size was estimated from the relation previously validated for total CPK as follows: (Infarct size) = (CPK released) x K x (body weight). K was calculated from MB activity measured in myocardium. The MB disappearance rate (k_d) was obtained from terminal portions of serum curves. MB CPK release (CPK_r) was calculated from hourly serum MB CPK values in 17 patients with infarction. Myocardial MB CPK averaged 121 $\pm$ 16 (SE, n = 7) IU/g. k_d averaged 0.2 $\pm$ .01%. Insignificant amounts of MB were detected in skeletal muscle, brain, intestines, lung, and kidney. With uncomplicated infarction, MB released into serum paralleled total CPK released. (CPK_r = (7.7 x MB CPK_r) - 4.5, n = 12, SD of slope = .6) and infarct size calculated from MB and from total CPK correlated closely (r = .97). With infarction complicated by shock, noncardiac CPK led to spuriously high estimates, and infarct size estimated from MB CPK was significantly less ($p < .01$, n = 5). Thus, analysis of serial changes in serum MB CPK activity permits accurate evaluation of the extent of infarction even in patients with shock accompanied by release of CPK from organs besides the heart.

SINUS NODE RESPONSES TO ATRIAL EXTRA-STIMULUS IN 36 PATIENTS WITHOUT APPARENT SINUS NODE DISEASE

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Thirty-six patients (pts) without sinus node disease were scanned with an atrial extra-stimulus (A_2) during sinus rhythm with sinus cycle length (CL) measured in msec. Zones of non-reset due to interference (ZNR), reset (ZR), interpolation (ZI), and sinus echoes (ZE) were defined by noting the timing of the first response following A_2. The zones were defined in terms of their longest and shortest A_1-A_2 coupling intervals (in msec). ZNR was found in 12 of 12 pts in whom A_2 was delivered late. Mean CL in these 12 was 779, with mean ZNR of 779 to 585 (25% of CL). All 36 pts (100%) had ZR. Mean CL in these 36 was 803 with ZR from 692 to 311 (47% of CL). Seven of 36 pts (19%) had ZI. Mean CL in these 7 was 739, with mean ZI of 344 to 279 (9% of CL). Four of 36 pts (11%) had ZE. Mean CL in these 4 was 855, with mean ZE from 350 to 313 (4% of CL). Calculated sino-atrial conduction time ranged from 40 to 153 (mean $\pm$ SEM of 92 $\pm$ 5 msec).

In conclusion, ZNR and ZR were found in all pts with normal sinus node function, while ZI and ZE were less common. Calculated sino-atrial conduction time was surprisingly long.

RUPTURE OF THE LEFT VENTRICULAR FREE WALL (LVFW) OR VENTRICULAR SEPTUM (VS) SECONDARY TO ACUTE MYOCARDIAL INFARCTION (AMI): AN OCCURRENCE VIRTUALLY LIMITED TO THE FIRST TRANSMURAL AMI IN A HYPERTENSIVE INDIVIDUAL

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Among patients (pts) with fatal AMI studied at necropsy, 23 had rupture of the LVFW and 18, rupture of the VS. The 41 pts ranged in age from 43 to 84 years (avg 60); 26 were men and 15 were women. The rupture occurred within the first 7 days in 29 pts. Evidence of previous systemic hypertension was present in 33 pts; at necropsy, however, cardiomegaly (heart weight > 400 gms) was present in 37 pts and all 41 had thickened LV walls. Only 3 pts had questionable historical evidence of previous AMI and 4, angina pectoris. At necropsy, only 3 pts had gross myocardial fibrosis and in each it was subendocardial. Prior congestive cardiac failure was absent in all 41 pts. At necropsy, the LV cavity was dilated in only 11 pts, and in each of them it appeared to have developed during the AMI. The AMI was anterior in 21 and posterior in 20 pts. Phonocardiographic and hemodynamic observations in 5 pts with rupture of the VS disclosed the following in each: wide (0.05 to 0.07 sec) splitting of the second heart sound; loud, usually holosystolic, murmurs decreasing in late systole because of reduced left ventricular ejection time indices (304-356 m/sec); atrial and ventricular filling sounds; and palpable thrills at the lower left sternal borders. In summary, rupture of the LVFW or VS is primarily a complication of systemic hypertension, of the first AMI, and of hypertrophied, previously well-contracting, hearts?

MITRAL VALVE ABNORMALITIES ASSOCIATED WITH TRANSPOSITION OF THE GREAT ARTERIES

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Increasing numbers of patients with transposition of the great arteries (TGA) are undergoing successful correction with Mustard's procedure. Although a success rate of over 90% has been reported, a knowledge of all associated lesions is desirable. For this study 163 specimens were examined. In order to determine whether the mitral valve annulus was small, its diameter was compared to that of the tricuspid annulus and length of left ventricle in the same specimen. In 38 hearts (23%) the morphology of the valve and diameter of the annulus was within normal limits. In 9 hearts (6%) the mitral valve was normal but the annulus was small. In 54 hearts (33%) the annulus was small and the valve normally formed except that chordae tendineae were attached to the midline of the anterior leaflet so that the free margin of the anterior leaflet was markedly shortened. In 62 hearts (38%) mitral valve anomalies were of 3 basic types: apposed papillary muscles due to underdevelopment of space between papillary muscles (56 hearts), poorly differentiated papillary muscles due to underdevelopment of space between papillary muscles and ventricular wall (2 hearts) and attachment of an indented anterior leaflet to the ventricular septum (4 hearts). A possible etiology for most of this spectrum is reduction in blood flow into the left ventricle in fetal life. Since the present study shows a higher incidence of mitral valve involvement than previously reported in TGA, greater clinical attention to mitral valve morphology by echocardiography and angiocardiography appears to be warranted.

EFFECT OF DIGOXIN ON ATRIOVENTRICULAR CONDUCTION: STUDIES IN PATIENTS WITH AND WITHOUT CARDIAC AUTONOMIC INNERVATION.

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The mechanisms by which digitalis effects atrioventricular (A-V) conduction have been a matter of controversy. To assess the effect of digoxin on A-V conduction, 5 patients with an intact cardiac autonomic nervous system (Group I) and 7 patients who had undergone cardiac transplantation and shown to be denervated (Group II) were studied before and one hour after 1.25 mg digoxin intravenous administration. Atrial and A-V nodal refractory periods were determined using the extra stimulus technique. Insignificant ($p>0.05$) decreases in the atrial effective refractory period (ERP) (from 262±12 to 254±11 msec) and atrial functional refractory period (FRP) (from 304±12 to 298±12 msec) were observed in Group I patients after digoxin. However, significant increases in the A-V nodal ERP (from 315±18 to 351±17 msec) ($p<0.05$), and A-V nodal FRP (from 426±42 to 460±46 msec) ($p<0.01$) were produced after digoxin. In denervated Group II patients, changes in atrial ERP (from 246±4 to 243±6 msec) and atrial FRP (from 311±12 to 316±11 msec) were also insignificant ($p>0.05$) after digoxin. In contrast to the Group I patients, digoxin induced changes in A-V nodal ERP (from 280±22 to 297±18 msec) and FRP (from 368±18 to 377±18 msec) were statistically insignificant ($p>0.05$). Our results demonstrate that the electrophysiologic effects of digoxin on A-V conduction are most marked in the A-V node and require cardiac innervation.

TREATMENT OF HYPERCHOLESTEROLEMIA IN YOUNG ADULTS WITH POLYUNSATURATED MEATS AND DAIRY PRODUCTS.

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The cholesterol(chol) lowering effect of polyunsaturates has been questioned. Therefore, the recent development of sunflower-soybean, protected lipid(PL) ruminant supplement permits the production of meats and dairy products containing increased linoleic acid(from 5 to 22%) and decreased palmitic acid(from 24 to 18%) and allows a new assessment of their dietary role. For 20 weeks the effects of diets produced from PL and conventional saturated fat (SF) ruminants were studied in 24 young adult couples, divided into 4 groups according to dietary sequence. Further each group was divided by median initial chol(170mg/dl) into high(H) and low(L). The variables were SF and PL meat and dairy products. The caloric and chol content of the diets were similar. Weekly dietary histories and controlled food distribution were used to assess caloric intake and diet composition. Twice weekly blood samples were analyzed for plasma chol and triglycerides(TG). Plasma chol values were:

Group	Diet	Pre-Diet (I)	1-10wks (I)	11-20wks (II)	P Values Pre-I	P Values I-II
AH	SF/SF	203.5±10.8	211.1±10.6	199.4± 9.3	<.05	<.005
AL	"	146.8±10.6	151.3± 8.5	145.6± 8.3	NS	NS
BH	PL/PL	187.5± 6.7	180.3± 4.4	173.2± 4.9	<.025	<.025
BL	"	148.4±17.7	150.3± 7.3	146.7± 5.0	NS	NS
CH	SF/PL	185.9±26.0	190.0±14.7	168.4±11.3	NS	<.025
CL	"	131.4±29.7	141.4±11.1	127.9± 9.9	<.025	<.005
DH	PL/SF	199.6±21.2	195.6± 8.8	205.7± 9.5	NS	<.01
DL	"	156.5± 7.4	157.1± 4.8	146.4± 7.4	NS	NS

Plasma triglycerides were not significantly changed by the diet. Therefore the PL diet provides a new, effective dietary treatment of hypercholesterolemia for a group at most risk for developing premature atherosclerosis.

REGIONAL PULMONARY FUNCTION IN CHILDREN WITH VENTRICULAR SEPTAL DEFECT AND PULMONARY ARTERY BAND.

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Surgical constriction of the pulmonary artery reduces pulmonary blood flow (PBF) in patients (pts) with VSD, but it may produce new physiological disturbances. We have studied regional distribution of PBF and ventilation using xenon-133, a gamma camera and a computer in 21 pts with VSD who had previous placement of pulmonary artery band (PAB).

Fourteen pts had normally related great arteries. Twelve of them had increased PBF to the left lung (mean 60.9 ± 5.3% of total PBF) and two were decreased (35 and 44%). The ventilation-perfusion ratio (V/Q) of the lung with higher flow was below normal (.77 ± .11). Six pts were restudied after operations at which the PAB was removed, the pulmonary artery widened with a patch, and the VSD closed. Postoperatively, the distribution of perfusion between the two lungs was normal in one pt, returned toward normal in three pts, and was unchanged in two. The V/Q of the lung with higher flow was .84 ± .15.

Seven pts had transposition of the great arteries with VSD and PAB. Five had an abnormally high flow to the left lung (mean 55.6 ± 3.5%) and two were low (30 and 36%). The V/Q in the lung with higher flow was abnormally low (.84 ± .14). The one pt in this group who was studied after corrective operation had no significant change from his preoperative values.

We conclude that PAB produces abnormalities of regional pulmonary function that may not be reversed by corrective operation.

(see Addendum)

ADAPTATIONS OF THE LEFT VENTRICLE TO CHRONIC PRESSURE OVERLOAD

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Eight trained conscious dogs were instrumented with a left ventricular (LV) micromanometer, pairs of ultrasonic crystals for measurement of LV wall thickness (WTh) and internal chamber diameter, and an inflatable cuff around the ascending aorta. Heart rate was controlled during each study by atrial pacing. After 3 control studies, the cuff was inflated. At an average of 11.4 days after aortic constriction, LV systolic pressure (SP) was 218±11mmHg (SEM) and the cross sectional area (CSA) of the LV wall (calculated from WTh at end diastole [ED]) was increased by 11 2% ($p<0.001$). In serial studies in 5 dogs, mean wall stress (WSt) at 11 days was increased to 205.2×10^3 dynes/cm^2 ($p<0.02$); ED internal diameter (EDD) was increased by 4% (control 33.0±2.7mm, $p<0.05$), and mean shortening velocity (Vcf) always decreased (average -24%) from a control of 1.41±0.18 circ/sec. In late studies (mean 3 wks), LVSP was maintained, wall CSA was further increased to 16±4% above control ($p<0.02$), and mean WSt fell to 180.3×10^3 dynes/cm^2; EDD had returned to normal, with consistent improvement of Vcf (average -16% of control). Therefore initial abnormalities induced by pressure overload improved as wall hypertrophy developed over 3 weeks. Immediately after release of the aortic cuff, WSt fell to 99.1×10^3 dynes/cm^2 and Vcf increased to 1.71±0.18 circ/sec ($p<0.05$). Twenty-four hours later both Vcf and peak dP/dt were unchanged from control. Thus, early after relief of chronic pressure overload, contractility measures were clearly normal, indicating that hypertrophy per se did not produce depression of myocardial inotropic state.

HELIUM THERAPY FOR THE PREVENTION OF VENTRICULAR FIBRILLATION FOLLOWING MYOCARDIAL INFARCTION

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Only one previous investigator, Pifarre, experimentally demonstrated the feasibility of using helium therapy for the prevention of ventricular fibrillation; regrettably, it was employed prior to circumflex coronary artery ligation. In our own laboratory, anticipating clinical application, helium therapy has been used to determine the efficacy of this treatment following ligation of the left anterior descending coronary ligation. Of 22 control dogs, 14 (63.6%) developed ventricular fibrillation within 2 hours of left anterior descending coronary ligation. Twenty dogs were administered a mixture of 20% helium, 30% oxygen, and 50% compressed air--10 min. prior to, during, or 10 min. subsequent to ligation. Only 1 dog, administered helium 10 min. subsequent to ligation, developed ventricular fibrillation, amenable to defibrillation with the application of a simple electrical countershock. Moreover, the extent of revascularization of the myocardium, determined by the Satinsky methylene blue technique, was apparently favored by helium therapy, beginning within 1 hour of ligation. Also noteworthy was the observation that animals treated with helium therapy experienced few premature ventricular contractions. This preliminary study indicates that the application of helium therapy subsequent to myocardial infarction is promising and warrants further intensive investigation.

TRANSIENT ASYMPTOMATIC ST SEGMENT DEPRESSION DURING DAILY ACTIVITY

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To evaluate ST segment changes during daily activity, a continuous (Holter) ECG monitoring study was conducted in 27 coronary artery disease patients with angina pectoris (AP). All had significant ST segment depression (>1mm) associated with AP with repeated treadmill exercise testing which preceded monitoring periods. During usual daily activities and treadmill exercise heart rate (HR), ST segment depression and level of exercise at AP were determined.

During 2736 hours of recording, 412 transient (<60 min) periods of significant ST segment depression were recorded. Although 367 AP episodes were reported, only 31% were associated with ST depression. The remaining periods of ST depression were not posturally related and occurred at HR significantly below that observed at angina during treadmill exercise (115 ± 5 vs 93 ± 4, $p<.001$). Furthermore, only 5% of all 702 ischemic bouts (AP, ST depression or both), occurred with activities having a predicted oxygen cost comparable to that determined, during repeated exercise testing, to evoke AP. Hourly nitroglycerin (NTG) reduced frequency of significant ST depression 58%, $p<.001$.

It appears that periods of transient ST segment depression occur very frequently during daily activities, usually without symptoms. These asymptomatic ischemic episodes occur at HRs and levels of activity not expected to evoke myocardial ischemia and can be prevented by NTG.

ANTIANGINAL RESPONSE OF CORONARY HEART DISEASE PATIENTS TO LONG TERM PERHEXILINE MALEATE

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To evaluate the antianginal effects of the new drug, perhexiline maleate, a double blind cross over study was undertaken in 15 patients (46-60 years old) with significant coronary artery disease documented by coronary arteriography. Each had at least 5 episodes of typical angina pectoris (AP) per week with significant ST segment depression during Holter Monitoring (DCG) and treadmill exercise. Monthly 10-hour DCGs, treadmill exercise studies,and detailed daily diaries were completed by each patient. After a 3 month observation period the patients were randomly given either placebo or perhexiline maleate for 3 month periods.

After 28 months, the number of AP episodes and nitroglycerin consumption per month during perhexiline decreased from 60 + 12 to 25 ± 10 and 51 ± 12 to 23 ± 8, respectively ($p<.001$). Exercise heart rate was reduced by perhexiline from 111 ± 3 to 105 ± 6 beats/min ($p<.05$) while exercise duration increased from 230 ± 30 to 305 ± 54 seconds ($p<.02$) before AP.During 2715 hours of DCG, the number of episodes of ischemic ST segment depression and AP decreased ($p<.05$) during perhexiline administration from 13.2 to 6.4 and 22 to 12 episodes per patient, respectively, compared to control.

These results indicate that perhexiline is useful in the long-term management of some patients with AP and additional long-term studies are warranted.

INCREASED SENSITIVITY TO LOW LEVELS OF ARM WORK IN PATIENTS WITH ISCHEMIC HEART DISEASE (IHD)

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The greater pressor and pulse rate responses to any given level of dynamic arm as compared to leg work is held responsible for the oft repeated history of keen sensitivity of angina to arm exercise. We compared maximal arm to leg work by means of progressive, symptom-limited bicycle stress tests in 33 males, mean age 51, with a spectrum of IHD, 7 of whom reported angina to be usually precipitated by arm rather than leg work. The end-points (ischemic ST depression, angina, or fatigue) were identical for the paired leg and arm tests in 30 of 33. Mean values ± standard error at end-point were:

Exercise	Total Work/ KPM	Max Heart Rate/min	Max Heart Rate x Syst BP/100
Leg	439 ± 30	129 ± 4	254 ± 11
Arm	181 ± 17	122 ± 4	234 ± 13
n=	33	33	25
p	<0.001	(Not Significant)	

Arm work tests were practical, diagnostic and obviously applicable to many patients unable to perform leg work. The performance of the 7 with a history of arm work sensitivity was not materially different from the others. The mean ratio of total arm to leg work at the end-points (thresholds for myocardial ischemia or exhaustion) in these patients was 0.41. This was far less than the work ratios achieved in studies of maximal performance of normal men. These data suggest disproportionate enhancement of pressor and heart rate responses at very low levels of dynamic arm work in patients with IHD regardless of history of arm work sensitivity.

MITRAL VALVE PROLAPSE IN CHILDREN: CLINICAL, ECHOCARDIOGRAPHIC, AND CINE-ANGIOGRAPHIC FINDINGS IN 81 CASES.

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Late systolic mitral regurgitation (LSMR) resulting from mitral valve prolapse is a unique form of mitral valve dysfunction. We have recognized LSMR in 81 children ranging in age from 4 to 17 years. Characteristic auscultatory phenomena, including striking postural variation, formed the basis for the clinical diagnosis in every case. Echocardiographic studies demonstrated abnormal posterior motion of one or both mitral valve leaflets during systole. Echocardiographic-anatomic correlation was obtained by cardiac catheterization and selective left ventriculography in 18 patients. An associated secundum atrial septal defect in 3 patients permitted direct visualization of the mitral valve during surgical closure of the atrial septal defect. A review of routine left ventriculograms performed in 55 additional patients with a secundum atrial septal defect failed to demonstrate mitral valve prolapse. It is evident, however, that the appearance of the mitral valve ring on left ventriculograms in patients with secundum atrial septal defect may lead to an erroneous diagnosis of mitral valve prolapse. This was substantiated by false positive cine-angiographic evidence when neither clinical or echocardiographic evidence of mitral valve prolapse was present. Subsequent surgical closure of the atrial septal defect failed to demonstrate abnormality of the mitral valve. It is concluded that mitral valve prolapse with late systolic mitral regurgitation is a common form of mitral valve dysfunction in children. Long-term follow-up in our patients has failed to demonstrate progression of mitral incompetence.

PRE-EXITATION SYNDROME AND AJMALIN.

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The effect of 50 mg of intravenous (i-v) ajmalin on the ECG and His bundle recording was studied on 22 patients with pre-exitation syndrome. 21 showed a prolongation of the P-R but not of the A-H interval, mainly due to the dissapearance of the delta wave, with normalization of the QRS time in 16 and prolongation in 5. In 14 cases there were modifications of the ΔQRS and T waves in the ECG. During a bout of supraventricular tachycardia in a case of WPW, at his bundle recording, an H deflection was inscribed preceding the QRS, just as it occurred previously under basal conditions with i-v ajmalin, which modified a typical pattern of WPW syndrome with H deflection appearing after the QRS. This suggest that at least in some cases the antegrade conduction during the bout of tachycardia is through the A-V node. These observations leads us to conclude that the main effect of ajmalin is exerted at the anomalous pathway site, prolonging its conduction time; which may be of practical value in the treatment of tachycardias, by blocking the reentrant circuit. Besides, the normalization of the ECG pattern under the effect of the drug, may be of value in the differential diagnosis of some necrotic or left ventricular hypertrophy pattern. Prolongation of intraventricular conduction in some cases, may be of potential dangerous effect.

EFFECTS OF UNILATERAL CARDIAC SYMPATHETIC DENERVATION ON THE VENTRICULAR FIBRILLATION THRESHOLD

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Electrical stimulation of cardiac sympathetic nerves lowers ventricular fibrillation threshold (VFT) while bilateral ablation of stellate ganglia (SG) increases it. However, our recent clinical and experimental data suggested that unilateral ablation of SG could affect VFT in a previously unsuspected way. In vagotomized dogs anesthetized with chloralose VFT was measured by stimulating the paced heart through epicardial bipolar electrodes with trains of 4 msec pulses at 100 Hz which scanned the entire vulnerable period. VFT was measured in control and after ablation or cooling of either SG. The latter produces total and reversible blockade of neural activity allowing alternation of trials with one or both SG functionally active. The reversibility eliminates the possibility of obtaining misleading results from nonreversible procedures, like stellectomy, which might in fact be due to changes in the animal's condition. The results with either technique were identical. In 7 dogs (4 with stellectomy and 3 with cooling) blockade of the right SG produced a significant decrease in VFT (-42%±9)($P<0.005$). By contrast, ablation of the left SG clearly increased VFT (+45%±11, 3 experiments). The results depended upon a high resting level of sympathetic activity. Our data suggest that the two SG may affect cardiac excitability by specific but different mechanisms. The protective effect of left SG ablation may explain why episodes of ventricular fibrillation were suppressed in 4 of 4 patients with the long Q-T syndrome.

SLEEP STAGES REGULATE ARRHYTHMIAS IN THE ISCHEMIC PIG HEART

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Two groups of purebred juvenile Hampshire pigs were implanted with left anterior descending coronary artery occluders and then adapted to the recording chamber until they would sleep in it. In the first group, permanent coronary occlusions were made and the effects of various sleep stages on the resultant cardiac arrhythmias observed. Sleep intervals during which transitional and slow wave (SW) sleep alternated were correlated with increased arrhythmias relative to the awake state ($p<.04$). The increase was maximized during sustained periods of SW sleep. Intervals during which rapid eye movement (REM) sleep predominated were correlated with a reduction in arrhythmias. In the second group, temporary occlusions were made during both an awake condition and during either SW or REM sleep. Occlusions during SW sleep reduced the ventricular fibrillation latency (VFL) compared to the awake control ($p<.05$), whereas occlusions during REM sleep increased VFL ($p<.05$). SW sleep, but not REM sleep, was concluded to have a deleterious effect on the ischemic myocardium. REM sleep apparently has a beneficial effect since it increases VFL. Heart rate changes did not appear to be correlated with the effects of either sleep stage.

THE ECHOCARDIOGRAM IN THE ASSESSMENT OF MITRAL VALVE AREA
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The purpose of this investigation is to examine the efficacy of using mitral valve slope as an index of surgical success following commissurotomy. Twenty-two patients with mitral stenosis had pre and post operative echocardiograms. Echocardiographic results were compared to pre and post commissurotomy valve areas as determined by Gorlin's formula for fixed orifices.

	Pre-op (σ^2)	Post-op (σ^2)
Average valve area (cm^2)	0.97 (0.17)	2.23 (2.97)
Average valve slope (mm/sec)	13.00 (49)	34.00 (152)
Correlation coefficient	0.28	-0.03

σ^2= variance

The results support the belief that echocardiographic mitral valve slope of less than 60 mm/sec is indicative of mitral narrowing. Following surgery the average value for mitral valve slope increased from 13 mm/sec to 34 mm/sec ($P<.002$) and the average valve area increased from 0.97 cm^2 to 2.23 cm^2 ($P<.002$). However, there is no significant correlation between mitral valve slope and calculated valve area, nor does the postoperative change in slope correlate with change in valve area (r=.27).

It is apparent from this study that echocardiographic measurement of mitral valve slope is not an accurate indicator of surgical success as judged by measurement of mitral valve area.

VECTORCARDIOGRAPHIC DIAGNOSIS OF ANTERIOR MYOCARDIAL INFARCTION
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Frank lead vectorcardiograms (VCG) from 4 carefully selected patient subgroups (228 patients) were analyzed to develop optimal criteria for the diagnosis of anterior myocardial infarction (AMI). Specificity was evaluated using 100 healthy volunteers under age 30 and 80 patients with normal left ventriculogram and normal coronary arteriograms. Sensitivity was determined using 25 patients with evolutionary ST-T wave (V_{1-2}), and LDH and CPK isoenzyme evidence of acute AMI; and 23 patients with isolated anterior wall asynergy and > 70% occlusion of the left anterior descending coronary artery. Patients with VCG evidence of Bundle branch block, left or right ventricular hypertrophy were excluded. The criterion which was found to give the highest sensitivity with> 95% specificity was: Initial anterior forces which are < 25 msec in duration and ≤ 0.1 mV in maximal anterior amplitude. The performance of this proposed criterion was then tested using 4 similarly defined patient subgroups consisting of a total of 224 patients. The proposed criterion was found to be statistically superior to both the VCG criteria of Hugenholz (initial .02 sec vector posterior) ($p < .05$) and to widely used ECG criteria for AMI ($p < .01$). The incidence of false positive diagnosis in these test subgroups was < 1% with a sensitivity of > 95%. Thus, these quantitative criteria for time and duration of initial anterior forces are both highly specific and sensitive indicators of AMI.

BALL VALVE PROSTHESES: LATE RESULTS. Albert Starr, MD, FACC, Lawrence Bonchek, MD, S. H. Rahimtoola, MD, FACC, Frank Kloster, MD, University of Oregon, Portland, Oregon.

Experience with aortic and mitral replacement (AVR and MVR) extends 9 yrs with current non cloth-covered ball valves (BV) (6120 mitral, 1200-60 aortic) and 6 yrs with cloth-covered BV 6310-20 mitral, 2310-20 aortic). Actuarial cumulative probabilities at 5 yrs in anticoagulated patients who survive operation are:

	MVR		AVR	
MODEL	6120	6310-20	1200-60	2310-20
No. Patients	64	171	132	116
Late Mortality	17%	20%	19%	19%
Reoperations	0%	4%	1%	8%
Ball variance	0%	0%	0%	0%
Emboli (Residual)	8%	1%	4%	0%
Emboli (No residual)	10%	2%	12%	0%
Alive-No complications	65%	73%	64%	73%

Since 1970, 134 patients had AVR with 2310-20 BV without warfarin. Actuarial probabilities at 3 years were unsatisfactory: 26% late death, 6% reoperation, 4% embolus with residual, 9% embolus without residual, and 54% alive without complications.

Non cloth-covered BV perform well, and we still use them in certain circumstances. Strut cloth wear, a major cause of reoperation in 2310-20 valves, is eliminated by a new cloth-covered "Track" valve, now under clinical evaluation.

Assessment of a prosthesis depends upon accurate long-term information, analyzed with sophisticated actuarial methods that facilitate comparisons with other valves. Reports of short-term follow-up can be misleading. Cloth-covered BV have eliminated emboli after AVR, but three yrs follow-up were necessary to demonstrate statistically the continuing need for anticoagulation.

VENTRICULAR PERFORMANCE MEASURED DURING EJECTION: THE RATE OF CHANGE OF POWER IN PATIENTS WITH ANGINA
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An expression representative of the rate of change of ventricular power during ejection was derived. It is:

$$\text{Rate of change of power (dynes-cm sec}^{-2}) = \dot{Q}\frac{dp}{dt} + p\frac{d\dot{Q}}{dt}$$

where p is ventricular pressure (dynes-cm sec^{-2}), $\dot{Q}$ is aortic flow (cm sec^{-1}), dp/dt and $d\dot{Q}/dt$ are their rates of change. It was applied to the evaluation of left ventricular performance of patients with angina. Performance was categorized as normal if the ejection fraction (EF) was above 58%, mean velocity of circumferential fiber shortening (V_{CF}) was above 1.3 sec^{-1}, and left ventricular end-diastolic volume index was below 90 ml/m^2. Performance was considered abnormal if EF was below 50% and V_{CF} was below 1.0 sec^{-1}. In those with normal performance, the rate of change of power was 27 ± 3 dyne cm $sec^{-2} \times 10^8$ (mean ± SE). In patients with abnormal performance it was 11 ± 1 dyne cm $sec^{-2} \times 10^8$ ($P < .001$). There was no overlap of values. Such a clear distinction was not observed with standard isovolumic indices. Peak dp/dt showed wide overlap, although the means differed ($P < .05$). Vmax and max 1/p dp/dt showed no difference between groups. Regarding established ejection indices, the peak rate of change of flow, intrinsic in the rate of change of power, also distinguished between groups ($P < .001$). The rate of change of power is advantageous because it relates expressions of fluid dynamic importance (energy, power) to cardiac function. It serves in an integrative fashion by incorporating terms previously shown to be of functional significance. The derivation is free of assumptions. It appears therefore, to be a meaningful and useful indicator of performance.

QUANTIFICATION OF LEFT VENTRICULAR WALL MOTION. Douglas K Stewart, MD; Harold T. Dodge, MD, FACC; Morris Frimer, MS., University of Washington, Seattle, Washington.

A quantitative method for the study of segmental left ventricular (LV) wall motion throughout the cardiac cycle has been developed using biplane cine angiography in the antero-posterior and lateral projections at rates of 60-80 frames/sec. Margins of the LV are traced on an X-Y digitizer and stored in a computer for playback and analysis. The system is programmed so that sequential frames are automatically aligned by superimposing the long axis of each silhouette permitting the normal displacement of the aortic valve. Local motion is described as wall movement toward the long axis as the percent of end diastolic dimension (EDD) along 10 hemiaxes for each plane.

In 20 subjects with insignificant coronary disease wall motion of the basal 3/5 of LV is greater for the anterior and lateral (57 to 68%) than for the inferior and septal walls (39 to 51%) and is completed earlier in systole (0.33 to 0.36 vs. 0.38 to 0.45 sec). At the apical 2/5, wall motion of the inferior, anterior and lateral surfaces is similar in extent (59 to 88%) and timing.

In 20 patients with ASHD abnormal wall segment motion has been classified by location, % shortening as compared to normal, time to maximum shortening, and the number of segments involved. 17 had hypokinetic or akinetic areas using the above normal standards and late contraction of such segments was common. Late contraction often occurred at a time when other segments were relaxing. These studies define a quantitative method of analyzing abnormal LV wall motion.

DETECTION OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH TECHNETIUM 99m GLUCOHPTONATE.
H.W. Strauss, MD., Jacques Rouleau, MD.,D. Rossman, MD., Bertram Pitt, MD., Johns Hopkins Medical Institution, Baltimore, MD.

Technetium 99m glucoheptonate (TG) has been found to be localized in areas of acutely infarcted myocardium in animals. TG was administered in doses of 10-15 millicuries to 13 patients between 5 and 48 hours after onset of chest pain. Scintiphotographs of the left chest were obtained between 30 minutes and 4 hours after injection in the right and left anterior oblique projection. Eight patients had definite ECG evidence of acute myocardial infarction on admission, the TG scan was positive in all. Five patients had equivocal evidence of acute myocardial infarction by ECG on admission, 2 had positive TG scans. Acute infarction was confirmed by serial ECG and creatinine phosphokinese (CPK) studies in these 2 patients. The remaining 3 patients had normal TG scans and did not prove to have acute myocardial infarction by serial ECG or CPK studies.

In the 10 patients with serial ECG and CPK evidence of acute myocardial infarction there was a good correlation between peak CPK values and the % of the left ventricular area accumulating TG. $r = 0.91$ $P < .01$ (peak CPK range 86-2270 units, % left ventricular area range 21-64%).

TG myocardial imaging is useful in the detection and estimation of the size of the acute myocardial infarction.

THE COST OF CARDIAC PACING
William S. Stoney, MD, FACC; William C. Alford, Jr., MD, FACC; George R. Burrus, MD; and Clarence S. Thomas, Jr., MD, FACC. St. Thomas Hospital, Nashville, Tennessee.

The patient with a permanent pacemaker faces continuous significant medical expenses for the remainder of his life. A review of the financial records of 15 patients paced for more than 4 years (average 73 months) was conducted to establish the basic monthly cost of pacing. Each pacemaker was replaced after 24 months of service. A total of 1096 paced months was reviewed which included 65 hospital admissions.

The total hospital expense was $93,400 and the total physicians' fees was $18,750. The cost per month was calculated for each patient and varied from a low of $71/month to a high of $129/month. The total expense for the 15 patients was $112,150 with an average cost per patient per month of $102.

It was found that only one half of the total expense was recovered by the hospital. The patient paid 6% ($5,200) and Blue Cross or other insurance paid 5% ($4,600). Medicare paid a total of 38% ($35,600) leaving an unpaid balance of 51% ($47,900). This was written off as a reduction of revenue by the hospital as a medicare allowance.

Permanent cardiac pacing increases the medical expenses of a patient by an average of $102 per month. Fortunately for the patient the majority of the expense is borne by Medicare or other agent. Unfortunately for the hospital a large portion of this expense is not recovered.

SERUM MYOGLOBIN LEVELS IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION
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A recently developed radioimmunoassay for myoglobin was used to determine serum myoglobin levels in patients with myocardial infarction. Blood samples were obtained from patients immediately upon admission to hospital, hourly for the next 12 hours and then at 24 and 48 hours after the onset of chest pain. The presence of myocardial infarction was documented by standard electrocardiographic and serum enzyme criteria. Serum myoglobin was undetectable in 23 control subjects. All 5 patients with acute myocardial infarction had myoglobinemia ranging from 46-200 ngm/ml in the first available specimen (4 to 7 hours after the onset of pain). The peak serum myoglobin concentration ranged from 152-880 ngm/ml and occurred at 7 to 10 hours after the onset of pain. On the other hand, the serum creatinine phosphokinase levels peaked at 17 to 33 hours. In 2 patients with severe chest pain without acute myocardial infarction, no serum myoglobin was detected. Thus, myoglobinemia is an earlier indicator of myocardial infarction than routine serum enzymes.

EXERCISE-ECG IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION BEFORE DISCHARGE FROM THE CCU

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Since beginning of 1972 exercise-ecg has been used as a routine for all patients with acute myocardial infarction/AMI/ prior to discharge from the CCU.Exercise-ecg was performed on 209 patients,average 18 days after the onset of AMI. Technique:Bicycle ergometer,stepwise increase of work load by 300kpm/min. every sixth minute. ECG in 3 precordial and 3 extremity leads, and heart rate were recorded continuously,and blood pressure measured every minute.The patients were encouraged to continue work until the limit of their physical ability.The reason for stopping exercise was in 121 patients fatigue,in 24 angina pectoris,in 26 dyspnoea,in 10 arrhythmias in 9 pronounced ST-elevation or depression,and in 19 various physical inabilities.The exercise loads varied from 300kpm/min.through 1 minute to 900kpm/min.through 6 minutes.Serious complications were never observed.ST-T deviations,indicating myocardial ischemia,were observed in 117 patients at rest,and in further 32 during exercise.Heart rate increased from an average of 80 to 129 beats/min.Systolic blood pressure from an average of 126 to 170 mmHg and the product: HRxSBP from 10,250 to 22,300 on the average. The exercise-ecg is an objective measurement of patients physical and response in terms of HR and BP.It provided a better basis for advising the patient regarding return to work.It also had a tremendous psychological importance on the overall rehabilitation program.

INABILITY OF HYPOTHERMIA TO PREVENT ANOXIC DAMAGE TO MYOCARDIAL PROTEIN SYNTHESIS

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Anoxia causes irreversible damage to myocardial protein synthesis while hypothermia causes reversible inhibition of the same process.

The effect of anoxia and additive hypothermia on residual myocardial protein synthesis (RMPS) was evaluated using ^{14}C-L-phenylalanine (^{14}C-phe) incorporation into total protein of isolated rabbit right ventricular papillary muscles (RVPM) in vitro. RVPM were incubated at 37°C and at 25°C in buffer under anoxia (95% N_2, 5% CO_2) for two to four hours and then reoxygenated (95% O_2, 5% CO_2) at 37°C for two hours with ^{14}C-phe present in the media for the final hour of incubation. ^{14}C-phe activity was expressed as mean d/m per mg total protein and as percent incorporation of paired oxygenated control RVPMs at 37°C.

^{14}C-phe incorporation in 12 paired muscles incubated for two hours was 38% of control (3,267 vs. 8,581 d/m control) following anoxia and 49% of control (4,166 d/m) following anoxia at 25°C ($P<0.05$). Similar results were obtained after four hours of anoxic and hypothermic intervention with 15 mM glucose present in the media.

It is concluded that depression of RMPS after two and four hours of anoxia was lessened but not prevented by hypothermic temperatures. Likewise the protective effect of high glucose concentration in the media on RMPS was not significantly enhanced by hypothermia.

RIGHT VENTRICULAR FUNCTION IN PRESSURE AND VOLUME OVERLOAD

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Study of Right Ventricular (RV) behaviour in congenital heart disease has been made using catheter-tip-micromanometers in the right and left heart to yield pressure and its first derivative and systolic time intervals. 12 patients (ages 12-35, bundle branch block excluded) were divided into physiological groups: RV pressure overload without pulmonary hypertension (PHT), 2 Fallot, 1 pulmonary valve stenosis; RV pressure overload with PHT, 2 Eisenmenger ventricular septal defect (VSD); RV volume overload without PHT, 2 atrial septal defect (ASD), 1 VSD; RV volume overload with PHT, 2 ASD; 2 normals. RV volume overload without PHT and normals behave identically. Left ventricular dp/dt maximum (max.) occurs before RV dp/dt max. and both these events occur after pulmonary valve opening. LV dp/dt max. > RV dp/dt max. In RV pressure overload with PHT RV dp/dt max. occurs before LV dp/dt max. and before pulmonary valve opening. The RV pre-ejection period (PEP) is prolonged. RV dp/dt max. > LV dp/dt max. In RV pressure overload without PHT RV dp/dt max. occurs with or before LV dp/dt max. but not before pulmonary valve opening. RV PEP is not prolonged. RV dp/dt max. > LV dp/dt max. In RV volume overload with PHT RV dp/dt max. occurs before LV dp/dt max. but not before pulmonary valve opening. RV PEP is prolonged. RV dp/dt max. > LV dp/dt max. Thus, when RV pressure overload is due to chronic elevation of the pulmonary resistance the RV behaves in these respects like an LV; when RV pressure overload is due to RV outflow obstruction or when RV pressure and volume overloads are combined the RV shows some features of LV behaviour but the two groups are separable. Changes in RV behaviour are not seen when the ventricle is only volume loaded.

PULMONARY HYPERTENSION WITH DIAZOXIDE AND MINOXIDIL

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Vasodilators are potent antihypertensive agents; recently however pulmonary hypertension was found to occur with their use despite the reduction in systemic pressure (BP). Because of its importance in regard to cardiac competence and possible long-term effects on pulmonary vessels, studies were done during both acute (diazoxide) and long-term (minoxidil) therapy in 18 patients with different degrees and types of hypertension. Diazoxide in 8 patients lowered BP and systemic resistance, increased cardiac output (CO) but raised pulmonary artery pressure by 26.4% ($p<.01$ with non-significant changes in pulmonary vascular resistance (PVR) or wedge pressure. Minoxidil use (9 patients) reduced BP in all (-39/-32 mm Hg, $p<.01$) but was associated with definite pulmonary hypertension (PAP>30/15 mm Hg) in six. In two this appeared to reflect cardiac decompensation. In four, however, it was related to increased CO; two of them were treated with propanolol which lowered both CO and PAP. One of the four developed progressive increase over 6 months in PAP (46/20 mm Hg) and PVR (2.7 units) with maintained good BP control (165/92), and no signs of cardiac decompensation. Thus vasodilator drugs may have different effects on the systemic and pulmonary circulation, and the resultant pulmonary hypertension may be of critical importance during treatment in some hypertensive patients.

"AGENESIS" OF DUCTUS ARTERIOSUS ASSOCIATED WITH THE SYNDROME OF TETRALOGY OF FALLOT AND ABSENT PULMONARY VALVE

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The syndrome of Tetralogy of Fallot (T/F) with absent pulmonary valve has been well described in the literature. Whereas the clinical manifestations of this syndrome are variable, there is a rather distinct group of severely affected infants who usually succumb early in infancy with signs of marked respiratory distress. The latter is attributed to marked bronchial compression caused by the massively enlarged pulmonary arterial trunk and its branches.

Four term infants with respiratory distress, massive cardiomegaly and a systolic and diastolic murmur in the newborn period are described. Cardiac catheterization and cine-angiocardiography confirmed the suspected diagnosis of T/F with pulmonary valvular insufficiency due probably to absent pulmonary valve and demonstrated massive dilatation of the pulmonary arteries. The infants expired at the age of three, five, thirty and 90 days respectively (one post-operatively). Autopsy revealed in addition to the usual components of this syndrome, (i.e. ventricular septal defect, infundibular stenosis, absent pulmonary cusps, dilatation of the right ventricle, massive enlargement of the main pulmonary trunk and its branches) no ductus arteriosus or its remnants. It is postulated that this, not previously reported, association of "agenesis" of ductus arteriosus with the severe form of this syndrome may be pathogenitically related and may explain the massive dilatation of the pulmonary artery.

MULTIFACTOR ANALYSIS OF DETERMINANTS OF ISCHEMIC RESPONSE TO STRESS TEST IN CORONARY DISEASE: ROLE OF DISTAL FLOW AND SEVERITY AND NUMBER OF STENOSES.

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Despite widespread usage of exercise testing(ExT) for diagnosis and prognosis of coronary artery disease(CAD), detailed information relating coronary artery anatomy and ExT is incomplete. Accordingly, 60 patients(pts) undergoing graded maximal(M) ExT who had CAD by selective coronary arteriography were studied. Positive(POS) MExT was defined as ≥1.0mm flat or downsloping ST-segment depression .08 second following the J point. Positive MExT were present in 19/24(78%) pts with 3-vessel disease(VD); 11/18 (60%) pts with 2-VD and 4/18(22%) with 1-VD. Severity of stenoses(S), distal opacification(DO) beyond S and collaterals (COLL) were scored: S, 50%(1), 50-75%(2), 76-90%(3), 91-99%(4), 100%(5); DO, absent(0), poor(1), fair(2), good (3); COLL, absent(0), minimal(1), fair(2), good(3), excellent(4). Comparison of POS with negative(NEG) MExT: number of S, 2.5 vs 1.9($p<.01$); severity of S, 9.8 vs 6.3($p<.01$); DO, 1.5 vs 2.4($p<.001$); COLL, 2.2 vs 2.1,(ns). The location(proximal, mid or distal) of S and ejection fraction (EF) were the same($p>.05$) in each group. A comparison of POS with NEG MExT in a subset of 9 pts with isolated left anterior descending(LAD) S was made: POS vs NEG, 3 vs 6 (33% POS); number of S, 1.3 vs 1.1(ns); severity of S, 5.6 vs 3.3,($p<.01$); DO, 1.3 vs 3.0($p<.01$); COLL, 3.6 vs 1.0 ($p<.01$). Thus, adequacy of distal flow estimated by DO relates closely to NEG MExT. The severity and number of S also relates to POS MExT. With isolated LAD-S, COLL are more common($p<.01$) with POS MExT. In conclusion DO, severity and number of S and number of VD are important determinants of POS MExT while COLL, EF and location of S appear unimportant.

REGIONAL MYOCARDIAL FUNCTION EARLY AND DURING THE HEALING OF ACUTE MYOCARDIAL INFARCTION

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Ten dogs were instrumented with a micromanometer, a cuff around the circumflex coronary artery, and pairs of miniature ultrasonic crystals placed in normal and ischemic segments of the subendocardium of the left ventricle. The dogs were studied in the basal, conscious state before coronary occlusion, and at 1 week (Wk) and 3Wks after myocardial infarction. In the normal segments, average end diastolic length (EDL) increased from 15.8±0.9mm (SEM) to 16.4±0.9 at 1Wk and to 17.1±0.9mm at 3Wk ($p<0.01$); the extent of active shortening (ΔL) increased from 3.6±0.4mm to 4.3±0.5 at 1Wk and to 4.8±0.5mm at 3Wk ($p<0.005$). In the ischemic segments, EDL was 17.1±0.8mm in control, 17.3±0.7 at 1Wk (NS) and decreased to 15.6±1.0mm at 3Wk ($p<0.001$); ΔL fell from 3.0±0.3 mm to 1.3±0.3 at 1Wk ($p<0.001$) and was 1.6±0.5mm at 3Wk ($p<0.001$). Compliance, the ratio of change in length to change in diastolic pressure, was unchanged in the control segment but fell in ischemic segments from a control of 0.23±0.04mm/mmHg to 0.1 ±0.02 at 1Wk and 0.04±0.1 at 3Wk ($p<0.005$). The reductions in EDL, ΔL, and compliance in the ischemic segments each were directly related to the percentage of scarring found on histologic examination of myocardial tissue ($r=0.8, 0.96$, and 0.83, respectively). It is concluded that with healing after myocardial infarction, normal myocardium shows progressive dilatation and increase in function. Ischemic zones show progressive reduction in segment length and compliance. The latter changes, and reduced shortening, must reflect tissue loss as well as scar formation which was shown to correlate directly with these functional abnormalities.

ELECTROPHYSIOLOGICAL EFFECTS OF AMIODARONE IN MAN

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Using His bundle recordings, the electrophysiological properties of Amiodarone were assessed in 23 patients, 15 mn after intra-atrial administration of 5 mg/kg body weight. The effects on sinus rhythm, atrioventricular (A-V) conduction, right atrium and right ventricle were studied. A-V nodal and His-Purkinje system (HPS) conduction time was measured during atrial pacing and refractory periods determined by the single test stimulus method. Following Amiodarone, the sinus cycle length increased in 18 patients by a mean of 105 msec, decreased in 3 (average 80 msec), showed no change in 2. A-V nodal conduction time (A-H interval) was prolonged at comparable rates in 20 patients (average 20 msec) and unchanged in 3. HPS conduction time (HV interval) remained constant. The effective refractory period (ERP) of the atrium lengthened in 15 patients (average 28 msec), shortened in 4 (25 msec), was unchanged in the remaining 4. The refractory periods of the A-V node increased in all patients in whom they could be determined : the ERP lengthened in 15/15 patients, the functional refractory period in 20/20 and the mean change was similar (approximately 70 msec). The relative refractory period of the HPS lengthened in 5/7 patients (average 31 msec), remained unchanged in 2. ERP of HPS was increased in 1/2 patients by 25 msec and no change was observed in the other. In 7 patients, Amiodarone, by delaying conduction in the A-V node, abolished intraventricular block following premature atrial depolarization. ERP of right ventricle prolonged in 11 patients (average 19 msec), shortened in 2 (10 msec) did not change in 10. Thus the data are consistent with the clinical observation that Amiodarone can be effective in the suppression of supraventricular and ventricular arrhythmias.

CINE ANGIOGRAPHIC DIAGNOSIS OF PATENT FORAMEN OVALE IN PARADOXICAL EMBOLISM: Gerald P. Tracy, M.D.; Harold Smulyan, M.D.; James L. Potts, M.D.; Robert H. Eich, M.D.; Lewis W. Johnson, M.D., F.A.C.C., SUNY at Upstate Medical Center, Syracuse, N.Y.

Paradoxical embolism (PE), while potentially lethal or disabling, is rarely diagnosed during life. The hallmarks of the diagnosis are unexplained arterial embolism, venous thrombophlebitis, pulmonary embolism and an intra-cardiac communication. The right-to-left shunt is usually through a patent foramen ovale (PFO).

Right atrial angiograms were performed in 15 patients (pts) during routine diagnostic cardiac catheterization to determine the anatomic characteristics of the intra-atrial septum. None of the pts had intra-atrial septal defects. At rest, right atrial pressure (RAP) was lower than pulmonary capillary wedge (PCW) but RAP equalled or exceeded PCW during the valsalva maneuver (VM) in all pts studied. Right atrial cine angiograms were performed in the left anterior oblique position to place the intra-atrial septum in profile. RAP increased during the modified VM during breath holding for angiography but did not increase further with injection of contrast. Three of 15 (20%) pts studied had angiographic evidence of PFO. Two of the three PFO pts had evidence of right-to-left shunt during VM as measured by continuous intra-arterial oxygen saturation. One of these pts had documented PE through a PFO, which was diagnosed by right atrial angiography and was confirmed at the time of surgical closure of the defect.

Patent foramen ovale may be diagnosed at the time of pulmonary angiography by a right atrial cine angiogram in the patients suspected of having PE. This adds little additional time or risk to the diagnostic procedure. The right-to-left shunt across a PFO probably occurs during angiography because of a modified VM.

NEW DIAGNOSTIC EVIDENCE OF MYOCARDIAL INFARCTION IN BODY SURFACE ISOPOTENTIAL MAPS

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Isopotential body surface maps at 1 msec intervals were obtained by computer processing 192 simultaneously recorded chest ECG leads. Maps were obtained in 84 patients with old myocardial infarction (MI) documented by classical ECG changes, or compatible ST-T changes with typical history and enzyme patterns, and in 76 normal subjects. There were 28 patients in the MI group with inferior wall infarction. In 8 of these patients the current ECG had returned to normal, or showed non-diagnostic abnormalities. The maps from normal subjects showed an initial positive potential in the anterior chest, followed by a negative potential which begins in the right shoulder region and then moves inferiorly and medially to the anterior chest. In maps of patients with inferior MI, the negative potential was present in the inferior portion of the map. The total body surface distribution, however, included more intense negative potentials on the upper right thorax, so pathologic Q waves were not present in leads II or AVF. This map pattern was present in all 8 patients with previous inferior myocardial infarction and normal current standard ECG's. This study indicates that the isopotential body surface map provides useful diagnostic information regarding inferior myocardial infarction, and shows the abnormalities even when the standard ECG has returned to normal or is non-diagnostic. 20 - 30% of patients with inferior myocardial infarction ultimately develop a normal or non-diagnostic ECG, and thus there are significant numbers of patients who may be benefitted by this improved diagnostic procedure.

MARKED DEPTH AND DURATION OF ST DEPRESSION AS INDICATORS OF EXTENSIVE CORONARY ARTERY DISEASE

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Delineating prognostically ominous coronary lesions - such as triple vessel disease and proximal left anterior descending (LAD) obstructions - noninvasively would be of considerable value. This study was designed to evaluate whether treadmill stress testing would facilitate selection of pts with advanced coronary disease (CAD); specifically, whether markedly abnormal ischemic responses could be used as indicators of severity of CAD. Among 59 consecutive pts with documented CAD having both maximal treadmill testing and coronary angiography, 15 (grp I) had normal exercise responses, 18 (grp II) showed 1-3 mm "ischemic" (flat or downsloping) ST depressions, and 26 (grp III) demonstrated marked (> 3 mm) ischemic responses. The grp III pts had statistically significantly higher incidences of triple vessel disease (18/26, 69%) and proximal LAD lesions exceeding 50% (24/26, 93%), compared with grp I (2 & 10 of 15 respectively) and grp II (6 & 12 of 18) ($p=.01$). Group III also manifested more extensive disease as judged by the scoring system of Friesenger, Page and Ross, with a score of 11 or more in 18 of 26; ($p<.01$). We conclude that marked depth of "ischemic" ST depression aids in identifying that subgroup of the coronary population with severe CAD; and, therefore, serves as a useful means of culling out pts with potentially serious prognosis who might benefit from coronary angiography and possible bypass surgery.

COLLATERAL CIRCULATION IN CHRONIC CORONARY DISEASE: EFFECTS ON SEGMENTAL LEFT VENTRICULAR CONTRACTILE FUNCTION. Louis A. Vismara, MD; Richard R. Miller, MD; Anthony N. DeMaria, MD, James M. Foerster, MD; Ezra A. Amsterdam, MD, FACC; Dean T. Mason, MD, FACC, U.C. Davis, Calif.

This study was designed to determine the efficacy of coronary collateral circulation in preserving left ventricular contractile activity in coronary artery disease. To control the factors of native coronary disease, only patients (pts) with 75-100% proximal occlusion of either the left anterior descending (LAD) (17 pts) or right coronary artery (RCA) (29 pts) were matched for the presence or absence of coronary collaterals. The 19 pts with collaterals were comparable in age (average 53.2 yrs) to the 27 pts without coronary collaterals (average 55.1 yrs; $p>.05$). Mean left ventricular circumferential fiber shortening (VCF) was similar ($p>.05$) in presence or absence of collaterals both in LAD (1.33 vs 1.35 circ/sec) and RCA (1.07 vs 1.27). Segmental mean velocity (SMV) was calculated by angio endocardial shortening at three equidistant minor axes (mid, proximal and distal). In LAD pts, anterior wall SMV averaged 0.60, 0.71, 0.64 circ/sec with collaterals and 0.48, 0.52, 0.60 without collaterals ($p>.05$). SMV in RCA pts without collaterals averaged 0.45, 0.42, 0.76 circ/sec and was not improved in RCA pts with collaterals: 0.62, 0.43, 0.76 ($p>.05$). Further, in these pts with matched coronary artery disease, presence or absence of collaterals did not differentiate ($p>.05$) average end-diastolic volume index (93 vs 89 cc), ejection fraction (0.59 vs 0.57) or stroke index (54 vs 51 cc). Thus, coronary collaterals do not enhance either overall left ventricular pump function or segmental wall motion in pts with coronary heart disease.

RESULTS OF MEDICAL AND SURGICAL MANAGEMENT OF HIGH-RISK *UNSTABLE ANGINA

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Controversy exists as to the management of unstable angina. In the past 3 years, 27 patients (all men, ave age 52 years) have been seen with high-risk, unstable angina, defined as angina lasting for longer than 30 minutes, with associated ischemia ST and T changes, while being hospitalized after being treated with isosorbide dinitrate and propranolol for more than 2 days. Seven received only medical treatment (MED) and 20 underwent coronary artery bypass surgery (CAB). Evidence of prior myocardial infarction (MI) was present in 16 of 27 (59%) (4 of 7 (51%) MED and 12 of 20 (60%) CAB) and MI within 3 weeks of CAB occurred in 5 of 20 (25%). Coronary angiography was undertaken without incident in 25 of 27 and all had significant 2 or 3 vessel coronary obstruction with left anterior descending obstruction in all and 8 (32%) had left main obstruction. Of the 7 MED, all have had MI and 6 of 7 have died (.2-13 months ave 5.2 months). Of the 20 CAB there was 1 operative death, no late deaths and MI, although 4 of 20 (20%) had electrocardiographic evidence of ischemic injury post-operatively. Good to excellent relief of angina has occurred in 18 of 19 CAB survivors (follow-up, 1-36 months; ave 10 mos). Results suggest that high-risk unstable angina is a serious illness, MED is not satisfactory, angiography can be safely undertaken, multi-vessel coronary disease is present and CAB can be performed with low risk and with expectation of good clinical results.

LEFT ATRIAL ENLARGEMENT: ECHOCARDIOGRAPHIC VALIDATION OF ELECTROCARDIOGRAPHIC CRITERIA

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The reliability of the electrocardiogram (ECG) in detecting left atrial enlargement (LAE) was evaluated in 334 patients (pts) using echography (echo) as a standard for comparison. ECG criteria in sinus rhythm (302 pts) were: duration of P wave in lead I or II $\geq$ 0.12 sec with or without abnormal P wave in V_1 (L); duration of negative terminal P in V_1/PR segment $\geq$ 1.0 (V_a); negative P terminal force in V_1 > 0.03 mm sec (V_b). Echo LAE criteria were: I- LA dimension > 4.0 cm; II- LA/aorta ratic > 1.17 with or without criterion I.

Echo Criteria	Percent of Patients — Pos. ECG L	V_a	V_b	Total	Neg. ECG	Total No. of Pts.
I (+)	53	7.0	9	69	31*	71
(-)	9	1.0	14	24 **	76	231
II (+)	45	6.0	13	64	37 *	104
(-)	6	0.5	13	19.5 **	80	198

* % false negative ** % false positive

Greater ECG specificity (81%) but lower sensitivity (64%) was observed when echo criterion II was utilized. ECG criterion V_b appeared unreliable regardless of echo criteria. Excluding V_b increased ECG specificity to 94% and diminished sensitivity to 61%. In 32 pts with atrial fibrillation (27 with LAE) coarse vs fine fibrillary waves were unreliable in predicting LAE. Using appropriate criteria the ECG appears to be a highly specific but less sensitive indicator of LAE.

EXTENT AND SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS DYING FROM CARDIOGENIC SHOCK OR CONGESTIVE HEART FAILURE FOLLOWING ACUTE MYOCARDIAL INFARCTION.

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Of 800 patients consecutively admitted to the coronary care unit because of acute myocardial infarction (AMI), 147 died within 8 weeks of onset of infarction (18.4%). Of these 92 p (63% of deaths) died from pump failure, including 68 p from cardiogenic shock (CS) and 24 p from congestive heart failure (CHF). CS became manifest within 24 hours after onset of AMI in 84% (57/68 p). Of these 94% (64/68 p) died within three days after AMI. Onset of CHF was randomly distributed over a 3 week period following AMI. Of these 71% (17/24 p) died within 1 to 8 weeks after AMI. The coronary arteries (CA) were studied postmortem by angiography and serial sectioning in 51 p (37 p with CS and 14 with CHF). In both groups there was a 75% incidence of severe disease (at least 75% occlusion) over a long segment of the left anterior descending artery (LAD). There were differences however in involvement of the other CA in the group with CS versus CHF. Three vessel disease (occlusion of 75% or more) was present in 68% (25/37 p) with CS, but only in 29% (4/14 p) with CHF ($p<0.02$). 64% (9/14 p) with CHF showed no or less than 75% narrowing of the circumflex artery. 64% (9/14 p) with CHF had severe local narrowing of the right CA. 71% (10/14 p) with CHF had two vessel disease or less, the LAD nearly always being severely affected over a long segment. In view of the extent and severity of CA disease long term success from circulatory assist and cardiac surgery seems very unlikely in p with CS. Only p with CHF might profit from these procedures.

TRANSPOSITION OF THE GREAT ARTERIES WITH INTACT VENTRICULAR SEPTUM AND PATENT DUCTUS ARTERIOSUS

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A persistent patent ductus arteriosus (PDA) with intact ventricular septum (IVS) was demonstrated by angiography in 34 of 118 infants with D-transposition of the great arteries (TGA) undergoing balloon atrial septostomy (BAS). Sixteen (14%) were considered angiographically large. These infants were distinguished clinically by early referral (median age 1.5 days) with tachypnea rather than intense cyanosis as a major sign. Cyanosis was slight in half the group; aortic O_2 saturation was high (median 60%, range 21-31%) for TGA with IVS but several infants with severe heart failure had marked unsaturation. Continuous murmurs and prominent pulses were noted in only 4 infants. Initial clinical improvement occurred following BAS, but 8 infants (50%) required early additional procedures to enlarge the interatrial communication (IAC) compared to 15% of infants with TGA and IVS in our clinic. Early spontaneous closing (8-18 days) of large PDA was documented in 6 infants and associated in several with sudden deterioration. Eight infants had successful total correction, 2 infants died shortly after BAS from extreme acidosis and 4 died during early atrial surgery. The infant with TGA, IVS and large PDA represents a difficult management problem because: 1) persistent large PDA can lead to unremitting congestive heart failure, 2) BAS appears to be less satisfactory as a palliative procedure in the large PDA group, 3) spontaneous or surgical closure of the large PDA can lead to rapid cardiovascular collapse in the absence of an adequate IAC, 4) hemodynamic and histologic data appear to link persistence of a large PDA with early pulmonary vascular obstructive disease in infants with TGA and IVS.

ANALYSIS OF THE HIS BUNDLE CATHETER PACING TECHNIQUE TO LOCALIZE CATHETER ELECTRODE RECORDING SITES

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Localization of electrode recording sites is critical in the interpretation of electrograms (EGs) recorded utilizing the His bundle catheter electrode technique. This study in canine hearts further tested the validity of bipolar pacing through the recording electrodes to localize the electrode recording site. Following cardiopulmonary bypass and a right atriotomy, selected tripolar electrode catheters, in turn, were inserted from the inferior vena cava and, under direct visualization, placed along the course of the specialized A-V conduction system (SAVCS). EGs were recorded through each electrode pair simultaneously with an ECG, and SAVCS EGs identified. Bipolar threshold and suprathreshold stimuli then were delivered through each recording electrode pair, each electrode alternately functioning as the + or - pole. If one or both recording electrodes were distal to the membranous septum, suprathreshold or threshold stimuli always produced ventricular pacing. Selective right bundle branch pacing never occurred. When the electrode pair was proximal to the membranous septum, suprathreshold stimuli usually produced simultaneous atrial and ventricular pacing, but threshold stimuli produced simultaneous atrial and His bundle pacing or just atrial pacing. Bipolar EGs recorded from tissue under each catheter electrode through an electrode probe with electrodes separated by 1 mm showed that usually only one catheter electrode of a recording pair was overlying the SAVCS. It is concluded that when using the His bundle catheter electrode recording technique, threshold pacing through the recording electrodes is a reliable index for localization of the electrode recording sites.

CROSS SECTIONAL ECHOCARDIOGRAM IN ASSESSING THE SEVERITY OF VALVULAR AORTIC STENOSIS

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Since M-mode echocardiography is severely limited in the assessment of valvular aortic stenosis (AS), 17 consecutive patients with catheterization proven AS and 20 normal subjects were examined using a high resolution (120 lines per frame) real time, cross-sectional, echocardiographic sector (30°) scanner. The patients ranged in age from 5 to 62. There were seven patients with severe AS, four with moderate AS and six with mild AS. Maximum systolic aortic cusp separation (aortic valve diameter) corrected for body surface area (AVD_c) was determined during long axis scanning through the aortic valve. In patients with severe AS, AVD_c averaged 4.7 mm (range 2.5-6.1 mm), with moderate AS the AVD_c averaged 6.6 mm (range 5.5-8.1 mm). In patients with mild AS, AVD_c averaged 10.3 mm (range 6.8-12.2 mm). In normal subjects AVD_c averaged 15.4 mm (range 12.4-18.2 mm). Plotting the 4 groups (severe AS, moderate AS, mild AS and normal) against AVD_c gave an r of 0.9009 and a p of < 0.001. In each case of AS abnormal motion of the valve leaflets was apparent in the real time presentation. In two cases of AS the aortic valve could not be recorded through the chest and a subxiphoid approach was utilized. This study indicates that high resolution, cross-sectional echocardiography offers a possibly improved non-invasive method for the diagnosis and quantitative assessment of valvular AS. It further demonstrates the sensitivity and flexibility of this relatively new echocardiographic system.

EFFECT OF DIGITALIS IN PATIENTS WITH PAROXYSMAL A-V NODAL TACHYCARDIA.

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Atrio-ventricular (AV) conduction (C), ventriculo-atrial (VA) C and mechanisms of tachycardia (t) were studied by programmed electrical stimulation before and after administration of digitalis (d) in 15 consecutive patients (p) suffering from paroxysmal AV nodal t. d was given as ouabain directly into the right atrium in a dosage of 0,75 - 1,25 mg. Following d: 1. All p showed lengthening of AV nodal transmission time and of the effective and functional refractory period (RP) of the AV node, 2. only 6 p showed lengthening of VA C time or increase in RP of the AV junction in VA direction, 3. the re-entry zone (REZ) during which t could be initiated shifted to longer atrial premature beat intervals, 4. in 7 p the REZ was completely abolished and in 5 p markedly narrowed, 5. the width of the REZ increased in one p and did not change in 2 p, 6. RR interval during t increased by 35 to 110 msec (9 to 30% of the original RR interval), 7. the effect of d was optimal at 45 minutes after administration.
Seven p were restudied after 2 weeks of chronic oral administration of d. The results correlated well with those obtained following intra-atrial administration.
We conclude: a) p with AV nodal t react differently to d, the effect being benificial however in the majority (12/15) of p, b) the effect of chronic oral administration of d can be predicted from the results following intra-atrial administration.

RESULTS OF PREGNANCY IN WOMEN WITH CONGENITAL HEART DEFECTS

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The problems and outcome of pregnancy in 181 mothers with congenital cardiac malformations have been studied to date; 372 pregnancies resulted in 279 live births. Most of these infants have been divided into 3 groups according to the mother's basic hemodynamic function: those with hypoxemia (24) = Group (Gr) A; pressure load (63) = Gr B divided into subgroup (1) 37 with left ventricular obstruction and (2) 25 with right ventricular obstruction without shunt; and volume load (174) = Gr C. Intrauterine growth retardation associated with relatively large placentas has been most common in the pregnancies of the cyanotic mothers in Gr A (15 of 17 live births). This was predicted by serial ultrasound determinations and low 24-hour urinary estriol and human placental lactogen analyses. Postnatal growth was moderately rapid but none exceeded the 50th percentile by 3 to 5 years. Development has been within the average range in most of the children. Congenital anomalies have been greatest in Gr B (33%) but cardiac defects alone have been found in 8% of Gr A, 11% of Gr B, and 5% of Gr C, the majority of them comparable to the maternal malformation. The major threat to the offspring appears to be maternal hypoxemia or outflow obstruction. Risk to the mother has been greatest with pulmonary hypertension, large flow, or aortic obstruction. Corrective surgery appears to minimize but does not abolish all these risks.

MONITORING TISSUE OXYGENATION OF THE HEART FOLLOWING MYOCARDIAL REVASCULARIZATION

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A polarographic technique for the continuous monitoring of myocardial tissue oxygenation was evaluated in dogs and used in patients undergoing aorto-coronary bypass surgery.

Three precalibrated micro-Clark type electrodes were implanted at various depths in selected areas and connected to a dual purpose electronic circuit, which allowed simultaneous recording of myocardial tissue oxygen tension (MqO_2) and electrical activity potentials (unipolar electrograms).

In 13 dogs, MqO_2 from 30 areas was studied in relation to changes in arterial oxygen content, cardiac output, aortic pressure, coronary blood flow and myocardial oxygen extraction. The best correlation was with regional coronary artery blood flow (r=0.92).

In 9 patients, MqO_2 was measured in 14 areas undergoing revascularization and monitored for two weeks postoperatively. In seven, MqO_2 rose in 12 areas from 4.6 ± 1.4 to 12 ± 4 mm. Hg ($p < 0.05$), paralleling an increase in regional coronary artery blood flow via an aorto-coronary bypass (108±12 ml./min.). MqO_2 recorded from two areas in two patients increased immediately, but dropped in the third postoperative day, failing to rise in response to oxygen administration. Concomitantly, the ST-segment of the unipolar electrograms rose from 1.2 ± 0.4 to 6 ± 1 mv. ($p < 0.005$). This preceded by at least 24 hours subsequent evidence of myocardial infarction by standard ECG and enzymatic methods.

This technique seems sensitive and reliable. It appears to be capable of anticipating acutely developing myocardial ischemia during the high risk early postoperative period following coronary surgery.

THROMBOLYSIN® TREATMENT OF ACUTE MAIN PULMONARY THROMBOEMBOLI

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Acute thromboemboli within the main pulmonary arteries and right heart chambers visualized by cardiopulmonary angiography cause two distinct hemodynmaic patterns.

ACUTE MAIN, IN EXTREMIS is characterized by clinical shock, a cardiac index of < 1.6 L/min/M^2 (Range 1.6-0.85), a right ventricular end-diastolic pressure of > 10 mmHg (Range 15-20) a pulmonary vascular resistance of > 750 dyne-cm-sec^{-5} (Range 750-1326).

ACUTE MAIN is characterized by systemic normotension to hypotension, a cardiac index of > 1.6 L/min/M^2 (Range 1.76-4.0) and a pulmonary vascular resistance of < 750 dyne-cm-sec^{-5} (Range 199-652)

In six ACUTE MAIN, IN EXTREMIS patients treated with a one-hour superior vena caval infusion of Thrombolysin® (streptokinase activated human fibrinolysin and profibrinolysin) shock disappeared within 120 minutes and there was only one hospital death and no late deaths. The cardiopulmonary hemodynamics and angiograms in all five survivors returned to normal prior to discharge.

In 16 ACUTE MAIN patients treated with superior vena caval Thrombolysin® there was only one hospital death and no late deaths, with the cardiopulmonary hemodynamics returning to normal in the 15 survivors prior to discharge.

The rapid thrombolytic effect of Thrombolysin® in reversing shock, right ventricular failure, and pulmonary vascular hyperresistance in 22 patients with acute thromboemboli within the main pulmonary arteries is documented by serial cardiopulmonary hemodynamic and angiographic studies.

MECHANISM OF IMPAIRED CONTRACTILE PROTEIN FUNCTION IN AORTIC STENOSIS: ALTERATIONS OF MYOSIN ATPASE ACTIVITY IN THE CHRONICALLY PRESSURE OVERLOADED CANINE LEFT VENTRICLE.

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To evaluate the fundamental changes in contractile proteins underlying disturbed left ventricular(LV) performance in clinical aortic stenosis, severe aortic banding was performed in twelve dogs to raise the peak systolic LV pressure 70% above normal as measured at the time of sacrifice. Contrary to mild pulmonary artery banding, there was no increase in enzymatic V_{max} values of K^+ activated myosin ATPase. In contrast, 6 weeks following aortic banding, LV myosin was depressed 12% below normal and by 16 weeks postoperatively, enzymatic V_{max} values were 60% below normal. Normal LV V_{max} was 0.84 μmoles PO_4/mg·min. Similar decreases in CA^{++} activated myosin V_{max} were also observed. The wet weight of the heart relative to body weight increased 30% above normal by 6 weeks postoperatively and was 50% above normal after 16 weeks of aortic stenosis. Mechanical LV V_{max} was depressed 20% below normal following 16 weeks of severe aortic stenosis. By mass spectrometry analyses of intramyocardial gas tensions, LV tissue was hypoxic at 16 weeks postoperatively: Partial pressure of O_2 was 8 while that of CO_2 was 94, compared to control measurements of PO_2 24 and PCO_2 45. These experimental studies of severe aortic stenosis demonstrate that marked LV systolic pressure overload results in depressed myosin enzymatic performance in the hypertrophied myocardium. This abnormality in contractile protein function is postulated to be important in the reduction of mechanical contractile state which occurs secondary to the chronic excessive hemodynamic burden on the left ventricle.

COMPARATIVE MECHANISMS OF VENTRICULAR UNLOADING BY SYSTEMIC VASODILATOR AGENTS IN THERAPY OF CARDIAC FAILURE: NITROPRUSSIDE VERSUS PHENTOLAMINE.

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Since improvement of low cardiac output in pump dysfunction by vasodilators depends on relative actions on left ventricular(LV) impedance and preload, nitroprusside(NP) was compared to phentolamine(PH) in 16 coronary patients (pts). NP(25-100 μgm/min) and PH(1.0-2.5 mg/min) were separately infused IV in each pt to effect equal↓ of mean brachial arterial pressure(MAP) with control hemodynamics allowed to return between the two agents; administration sequence was alternated in successive pts. After MAP↓ (87 to 71 mmHg) with each agent, peripheral vascular resistance(TPVR 1386 dynes-sec-cm^{-5}) was unchanged after NP ($p > .05$) whereas↓ occurred with PH(-350; $p < .05$). In 16 pts, LV end-diastolic pressure(EDP 14 mmHg) was↓ more by NP than PH(-8 versus -5; $p < .05$); while cardiac index(CI 2.51 L/min/M^2)↓ with NP but↑ with PH(-0.32 versus +0.23; $p < .01$). In 9 normal EDP(≤12 mmHg) pts, NP↓ both EDP(-5) and CI (-0.40), whereas PH↓ only EDP(-3). In 6 high EDP(>12) pts, NP↓ EDP from 21 to 8(-13) without change in low CI(2.26); in contrast EDP↓ was less(-9) while CI↑ (+0.39, $p < .02$) with PH. Afterload/preload change expressed as ΔPVR/ΔLVEDP was greater with PH than NP(-190 versus -33; $p < .05$) in 16 pts. Equal LV afterload↓ by NP causes greater preload↓ than PH due to NP-venodilation which may counterbalance NP impedance↓ effect, thereby inhibiting CI rise. Vasodepressor-induced reflex competes with direct NP action which impairs impedance↓, whereas PH blocks alpha receptor stimulation. PH principally↓ afterload and NP has combined pre- and afterload↓ actions. Thus PH is more effective than NP in improving pump failure when LV does not remain fully preloaded at apex of its function curve.

DETAILED ANALYSIS OF AMBULATORY ARRHYTHMIAS IN PATIENTS WITH MITRAL VALVE PROLAPSE

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Since patients (pts) with mitral prolapse frequently have arrhythmias (A), 24 unselected and untreated pts were monitored with 24 hr ambulatory ECG recordings to characterize these A. 18 pts had PVC's ranging from 3 to 14,800 in 24 hrs. These 18 pts formed 2 distinct groups. 6 had infrequent (<50/24 hrs) PVC's and only 1 of the 6 had complex ventricular A (bigeminy). 12 had frequent (>400/24 hrs) PVC's and all 12 had complex ventricular A. All 12 had pairs, 8 had bigeminy, and 5 had ventricular tachycardia. 58% of the pts with frequent PVC's showed a statistically significant reduction in PVC's during sleep and 17% showed an increase. 15 of the 24 pts had APC's ranging from 3 to 9,190 APC's/24 hrs. 7 pts had episodes of supraventricular tachycardia (SVT). Complex atrial A's were distributed among the 15 pts with APC's without relation to the total number of APC's in 24 hrs. Sleep reduced the APC frequency in 77% of pts with frequent APC's. All episodes of SVT were brief and self-limited. There was a poor correlation between symptoms recorded on the pt log and A's detected on ECG. We conclude that pts with mitral prolapse and ventricular A fall into 2 distinct groups, those with infrequent PVC's and those with frequent PVC's and complex A. Those pts with atrial A represent a continuum. Sleep generally decreases A in pts with prolapse but a few pts show no change or increase. Finally, symptoms reported by these pts are not necessarily due to A.

DETERMINANTS OF FAST AND SLOW PATHWAY CONDUCTION IN PATIENTS WITH DUAL A-V NODAL PATHWAYS

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Electrophysiological studies were performed in two patients (pts) with documented paroxysmal supraventricular tachycardia (PSVT) and dual A-V nodal pathways as defined by atrial extra-stimulus (A_2) technique. In pt 1, the fast pathway (FP) was utilized during sinus rhythm (A-H of 100 msec). At paced rates between 110 and 140/min, the pt maintained either FP conduction (A-H of 125-185 msec) or slow pathway (SP) conduction (A-H of 360-420 msec). The coupling interval (CI) of the first paced beat determined whether that beat and all subsequent beats of a paced sequence utilized FP or SP. If the CI was longer than the FP effective refractory period (ERP) of 365 msec, FP conduction was maintained. If CI was equal to or shorter than the FP ERP, SP conduction was maintained. All SP beats (either induced by A_2 or during constant atrial pacing) were accompanied by minor QRS notching without change in H-V. Pt 2 manifested A-H of either 160 msec (FP) or 260 msec (SP) during sinus rhythm (NSR) at a cycle length (CL) of 500 msec. With NSR and FP conduction, shift to SP was achieved with CI of 400-375 msec (FP ERP). With NSR and SP conduction, resumption of fast pathway conduction occurred following an A_2 blocked proximal to H (CI of 290 to 260 msec). During NSR with either SP or FP conduction, atrial echoes with PSVT always occurred at CI of 365-300 msec, which induced an SP A-H of 320 msec or greater. In conclusion, the occurrence of both FP and SP conduction at identical CL, depends upon a long FP ERP (relative to CL). Sustained SP conduction at rates at which FP conduction can occur, probably results from repetitive retrograde concealed conduction to the FP. PSVT occurs when SP delays are sufficient for FP recovery (for retrograde conduction). Shift from FP to SP may result in changes in ventricular activation.

CLINICAL AND ECHOCARDIOGRAPHIC ASPECTS OF ASYMMETRIC SEPTAL HYPERTROPHY.

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Recent studies have suggested that asymmetric septal hypertrophy (ASH) is the most characteristic feature of idiopathic hypertrophic subaortic stenosis (IHSS) and that this abnormality can be detected echocardiographically (echo). We have analyzed the clinical and echo characteristics of 44 patients (pts.) with echo ASH observed over an 18 month period. IHSS was obvious clinically in only 20 pts. There was an equal male-female incidence. Age range was 17-77, 1/3 over age 60. Symptoms (Sx) of CHF were present in 25, angina in 21, 4 had no Sx with only a murmur. Physical examination was characteristic of IHSS in 10; 19 had normal (nl) carotids, and 4 had no murmur. Hypertension was found in 18. EKG showed LVH in 26, pathologic Q waves in 5, nl in 4. Chest x-ray showed cardiomegaly in 26 with marked enlargement in 8. Mitral valve abnormalities by echo were present in 39; diminished diastolic slope (32), systolic anterior motion (24). Echo ejection fractions were $>60\%$ in 41, (mean 83%).

Conclusion: Echo ASH identifies a large group of pts. with hypertrophic cardiomyopathy, some of whom have classical IHSS. Others may have severe cardiac Sx but lack clinical features typical of IHSS.

TREATMENT OF DIGOXIN TOXICITY WITH ACTIVATED CHARCOAL

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Evidence exists that activated charcoal by a process of adsorption can reduce systemic absorption of poisons by the gastrointestinal tract. Since digoxin participates in the enterohepatic circulation it should be possible to remove some of the drug through the same process. Ten dogs were used in the study. Four dogs received toxic amounts of digoxin (0.05 mg/lbs) intravenously while another group of four dogs received 0.02 mg/lbs by the same route. The remaining two dogs received 0.03 mg/lbs of digoxin orally. Following administration of the digoxin, blood and urine samples were assayed for digoxin at hourly intervals for a period of 8 hours. Additional assays were done at 24, 48, 72 and 96 hours. Electrocardiograms were obtained at the same time periods. A radio-immunoassay kit using iodinated digoxin was used for the digoxin measurements. The experimental protocol was repeated on the same animals four weeks later, adding activated charcoal through a nasogastric tube. Thirty grams of Norite A charcoal was administered 15 minutes before and 2 hours after the administration of intravenous or oral digoxin. Animals treated with activated charcoal did not manifest toxic symptoms such as vomiting and arrhythmias. In the dogs treated with activated charcoal there was a persistent lowering of serum and urinary digoxin levels. In those animals that received digoxin by the intravenous route there was a 25 - 35 per cent decrease in serum digoxin levels. A decrease of 75 per cent in the serum digoxin level was found in the dogs that received the drug by the oral route. Activated charcoal should be used in the treatment of digoxin toxicity.

LONG TERM RESULTS OF SURGERY FOR LEFT MAIN CORONARY ARTERY STENOSIS.

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130 patients with greater than 75% stenosis of the left main coronary artery (LMCA) had coronary surgery with saphenous vein or internal mammary artery bypass during a 4 year period from Jan. 1970 to Dec. 1973. Patients with valvular heart disease and ventricular aneurysm were excluded. All patients had symptoms of angina pectoris. 59 patients (45%) had greater than 90% stenosis of the LMCA and an unstable anginal pattern. No deaths resulted from selective coronary arteriography. Multiple bypass grafts were performed on all but 4 patients. Internal mammary to coronary artery bypass was used in 34 patients. The operative mortality for the group was 9.3% (12 of 130 patients). The operative mortality was 11.5% (8 of 69 patients) during 1970-1971 and 6.6% (4 of 61 patients) during 1972-1973. There have been only 5 late deaths at 3, 4, 6, 8 and 20 months. 95% of surviving patients are improved and 65% are free of angina pectoris. Post-operative catheterization studies in 45 patients showed that graft patency and improved exercise hemodynamics correlated directly with symptom relief. 113 patients (87%) are alive from 12 to 48 months after surgery. Survival statistics will be compared with published data from other centers on non-operated patients with LMCA stenosis. These findings would indicate that coronary surgery provides both symptom relief and improved survival in patients with severe left main coronary artery stenosis.

RELATIONS BETWEEN APRINDINE CONCENTRATION [APR], HEART RATE, ISCHEMIA AND VENTRICULAR FIBRILLATION (VF) IN DOGS

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APR, a new antiarrhythmic agent with local anesthetic properties, prevented arrhythmias in some dogs with acute left anterior descending coronary artery ligation, (LAD Lig), but was associated with a high incidence of VF in others. The purpose of this study was to explain this discrepancy. Experiments were performed on closed and pentobarbital-anesthetized open-chest dogs following APR administration. The sinus node was crushed and atrial pacing controlled the heart rate in the open-chest dogs. The following results were obtained:

#Dogs Open	Aprindine Dose	LAD Lig	Rate	VF
6	None	Yes	200	0/6
6	2-3 mg/Kg IV	Yes	200	5/6
6	2-3 mg/Kg IV	No	200	0/6
6	2-3 mg/Kg IV	Yes	<200	0/6
6	1.4 mg/Kg PO	Yes	200	1/6
3	5.6 mg/Kg PO	Yes	200	2/3

Closed-chest dogs received 6-7.5 mg/Kg APR PO. Following balloon-induced LAD Lig, 5/19 developed VF, at a mean sinus rate 152 beats/min. 14/19 had no VF, and had a mean sinus rate 108 beats/min. Initiation of VF required a critical myocardial [APR] plus a rapid heart rate plus ischemia. Omission of any factor prevented VF. A high [APR] preferentially binds to the myocardium immediately after the IV dose when serum [APR] represents only 1-2% of total dose. Myocardial [APR] then falls rapidly and after 1 hour VF can no longer be produced. Results suggest that rapid rate plus ischemia plus high myocardial [APR] produce asynchronous ventricular excitation leading to VF.

ADDENDUM

LATENT VIABILITY OF ISCHEMIC MYOCARDIUM

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The response to post-extrasystolic potentiation (PESP) was evaluated as a means of detecting and quantitating latent viability of ischemic myocardium in 11 mongrel dogs. A Hg-in-silastic length gauge was sutured to the anterior epicardial surface of the left ventricle (LV); LV pressure was determined by a catheter-tipped transducer and maintained by volume manipulation. The anterior descending artery was then ligated, and premature atrial contractions were introduced via an external stimulator. Within 2-3 min after occlusion shortening during ejection decreased an average of 81%±8, from 1.30±0.29 mm to 0.32 ± 0.05 mm. In every dog, PESP initially induced a marked restoration toward normal segmental contraction. Systolic shortening increased significantly to 1.14±0.23 mm, representing an improvement in shortening to 105%±12 of the preischemic control state. Additionally, paradoxic systolic expansion, when present, reverted to a normal pattern of contraction during PESP. Responsiveness to PESP deteriorated linearly with time over 2 hours following occlusion until the muscle became totally unresponsive to this intervention. Arterial reperfusion at this time or at 3 hours after loss of responsiveness revealed that the muscle segment was capable of returning to function. It is concluded therefore that a single premature atrial beat used to induce PESP provides a sensitive index of latent viability of non-contracting, ischemic myocardium. Loss of responsiveness to PESP represents a further definition in the progression to nonviability after loss of contraction. Thus, after ischemic muscle becomes unresponsive to contractile stimuli, it may remain viable but "comatose" for a substantial time.

CROSS-SECTIONAL ECHOCARDIOGRAPHIC EVALUATION OF MITRAL VALVE PROLAPSE IN CHILDREN

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The cross-sectional echocardiographic features of mitral valve prolapse (MVP) were defined in 16 children (aged 3-18 years). Real time multiple crystal echo studies were visualized in the cross-sectional mode and single crystal M-mode recordings were selected from the array. Fifteen patients displayed a prominent systolic posterior arching of the anterior mitral leaflet (AML) and a posterior mitral leaflet (PML) which was driven posteriorly against the atrio-ventricular junction. In 2 patients both AML and PML prolapsed into the left atrium. A whipping motion pattern of the AML was visualized in 3 patients. The MV leaflets themselves appeared abnormally thickened and rolled in 6 patients, 2 of whom had Marfans syndrome. Single crystal recordings selected from the array showed: 1) ease of identification of the level of maximal prolapse for the recording of the classical M-mode findings, 2) that the whole spectrum from discrete late systolic to holosystolic "hammock-like" prolapse could be demonstrated in most patients by recordings at different positions, and 3) the recording of multiple systolic lines from the MV complex occurred at a level where the ultrasound beam intersected the arched leaflets more than once. This new cross-sectional approach significantly enhances the noninvasive echocardiographic detection of MVP and provides an explanation for many of the single crystal observations reported previously.

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The President's Page: Excellence in Cardiovascular Practice—1975

By the time this letter is published, many will be making final arrangements to attend the 24th Annual Scientific Session of the American College of Cardiology in Houston, Texas. Robert J. Luchi, MD, FACC, Houston, the Scientific Program Chairman, and the Local Arrangements Co-Chairmen, Don W. Chapman, MD, FACC and Robert J. Hall, MD, FACC, also from Houston, are putting on the final touches for the best program yet. I am convinced that it will be an excellent learning experience. It will also be an excellent opportunity to renew former acquaintances and make new friends. Mrs. Denton A. (Louise) Cooley is arranging a number of exciting events for the ladies. They won't mind if men also attend.

A lot of things happen at an Annual Session of the American College of Cardiology . . . from the Presentation of the Colors at the Opening Session to the last paper presented on Thursday afternoon.

One of the highlights will be the Convocation on Wednesday, February 12, 1975. The new Fellows of the ACC, gowned in academic regalia, will receive the designation FACC. Some have said that the Convocation is an archaic ceremony, and at one time I was not too impressed with the practice. For the last few years, however, I have been pleased that this custom of the College has been preserved. I believe that in times such as these there is a real need for stability and tradition. The Convocation is a time when one can withdraw for a few minutes for introspective contemplation.

In past years, distinguished scientists and community-minded leaders have been recognized at the Convocation by the Board of Trustess of the College. This year is no exception. The College will recognize the following:

Richard Langendorf, MD, FACC and Alfred Pick MD, FACC of the Michael Reese Hospital and Medical Center, Chicago, Ill. have been selected as Gifted Teachers. President-Elect Charles Fisch, MD, FACC of Indianapolis will be their Marshal and point out that few American cardiologists who can interpret complex electrocardiograms have escaped the influence of these two dedicated teachers. If the team of Pick and Langendorf has helped you, join us in thanking them.

Arthur C. Guyton, MD, Professor and Chairman, Department of Physiology, University of Mississippi, Jackson, will be elected to Honorary Fellowship in the ACC. He has repeatedly distinguished himself by uncovering facts that have been unknown regarding cardiovascular adjustment in health and disease. Former ACC President and Honorary Trustee, George R. Meneely, MD, FACC of Shreveport, Louisiana will be his Marshal.

Former ACC President and Honorary Trustee, William A. Sodeman, MD, FACC of Toledo, Ohio will be designated a Distinguished Fellow. ACC Past President, Honorary Trustee, Distinguished Fellow and Gifted Teacher, George C. Griffith, MD, FACC, La Canada, California, will be his Marshal and describe his many accomplishments . . . President of the ACC, President of the ACP, etc.

The continuing contributions in government as well as science of ACC Trustee Theodore Cooper, MD, FACC, Bethesda, Maryland will be particularly recognized. Dr. Cooper will receive the Distinguished Service Award. Past President and Distinguished Fellow, Eliot Corday, MD, FACC, Los Angeles, will be Dr. Cooper's Marshal. Join with me in paying respect to this distinguished public servant.

The President of the College can recognize a person for special attributes. I am pleased to announce that ACC Executive Director, Mr. William D. Nelligan, will be given the Presidential Citation. I have selected ACC Past President, Honorary Trustee, Gifted Teacher and Distinguished Fellow, Dwight E. Harken, MD, FACC of Boston to be his Marshal.

We are fortunate that Mr. Leon Jaworski, Past President of the American Bar Association and Former General Counsel for the Justice Department assigned to investigate the Watergate scandal, will deliver the Convocation Lecture. He will therefore become a Convocation Medalist. A long-time friend and former ACC Governor of Texas, Don W. Chapman, MD, FACC, will be Mr. Jaworski's Marshal. Mr. Jaworski says he has no interest in discussing the Watergate hearings, and so he won't. His remarks, however, will be timely, precise and persuasive and yet they will be warm. Mr. Jaworski is indeed a *gentle man* and he does the College membership a great honor in addressing us.

The Convocation will be followed by a Dinner Dance. At that time we will recognize others who have contributed greatly. The program at the Dinner Dance will be light and friendly. Won't you and your spouse join us?

I could highlight many other features of the program. I am sure that you have seen that the program covers the broad field of cardiology. Paul A. Ebert, MD, FACC of San Francisco, has put together a complete program that will be of benefit to cardiovascular surgeons. I have sent the suggested program to that segment of our membership. Similarly, ACC Trustee Sam Kaplan, MD, FACC of Cincinnati has put together a complete program of interest for the pediatric cardiologist. This, too, has been sent to the appropriate members.

Also of particular interest is a meeting of the Directors of Adult Cardiovascular Training Programs on Sunday afternoon, February 9, 1975. Special attention will be directed to the cardiology manpower needs of the country. This discussion will consist of a critical evaluation of the needs . . . both numerically and by type.

If you have not planned to attend, why not make plans immediately? I welcome you to my home town . . . Houston, Texas. As a bonus, you might obtain "Excellence in Cardiovascular Disease—1975."

Henry D. McIntosh, MD, FACC
President
American College of Cardiology

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and various other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education in the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

JAN. 12–14 **Cardiologic Debates.** John H. Vogel, FACC, director and Bruce C. Paton, FACC and James S. Forrester, co-directors. Opticon Theater, Snowmass-at-Aspen, Aspen, Colo.

FEB. 10–13 **Twenty-Fourth Annual Scientific Session.** Henry D. McIntosh, FACC, president. Albert Thomas Convention and Exhibit Complex, Houston, Texas.

MAR. 6–8 **Cardiovascular Disease—1975: Practical Diagnosis and Management.** John Ross, Jr., FACC, Robert A. O'Rourke, FACC and Richard A. Carleton, FACC, directors. Sheraton Harbor Island Hotel, San Diego, Calif.

MAR. 13–14 **Core Curriculum: Cardiovascular Physiology: Clinical Utilization of Invasive and Non-Invasive Measurements.** James S. Forrester, director and H. J. C. Swan, FACC, co-director. Cedars of Lebanon Hospital, Los Angeles, Calif.

MAR. 17–20 **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. The Children's Hospital, Children's Hospital Medical Center, Cincinnati, Ohio.

MAR. 24–28 **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC, director. Indiana University Medical Center, Indianapolis, Ind.

APR. 7–16 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Sante Fe Inn, Rancho Sante Fe, Calif.

APR. 14–18 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Richard Gorlin, FACC, Michael V. Herman, FACC and Louis E. Teichholz, co-directors. Mount Sinai Medical Center, New York, N.Y.

APR. 16–18 **Echocardiography for the Clinician.** Joseph K. Perloff, FACC, Nathaniel Reichek and Morris N. Kotler, FACC, directors. The University of Pennsylvania Medical Center, Philadelphia, Pa.

APR. 22–24 **Optimal Standards of Care in Cardiac Emergencies.** Albert N. Brest, FACC, director. Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa.

APR. 30 to MAY 2 **Core Curriculum: Vectorcardiography: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

MAY 5–8 **Current Concepts in Cardiology—1975.** Philip R. Akre, FACC, director and Masato Takahashi, FACC and John A. Bowers, co-directors. Caesars Palace, Las Vegas, Nev.

MAY 10–11 **Core Curriculum: Clinical Vectorcardiography 1975.** Irwin Hoffman, FACC and Robert I. Hamby, FACC, directors. Americana Hotel, New York, N.Y.

MAY 12–15 **Cardiology for the Internist.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 16–18 **Core Curriculum: Myocardial Biology in Health and Disease—1975.** Arnold Schwartz, FACC and Mark L. Entman, directors. Holiday Inn-Medical Center, Houston, Tex.

MAY 29–31 **Ischemic Heart Disease: A Critical Overview.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Golden Gateway Holiday Inn, San Francisco, Calif.

JUNE 4–7 **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

JUNE 5–7 **Progress in Coronary Artery and Valvular Heart Disease.** S. H. Rahimtoola, FACC, director. University of Oregon Medical School, Portland, Ore.

AUG. 23–25 **Tutorials in the Tetons (Cardiac Emergencies).** Robert S. Eliot, FACC, director and Robert J. Davis, FACC, Alan D. Forker, FACC and Vincent F. Miscia, FACC, co-directors. Jackson Lake Lodge, Jackson Hole, Wyo.

REVIEWS IN CARDIOLOGY*

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ANGIOTENSIN

Specific inhibition of the renin-angiotensin system: A key to understanding blood pressure regulation. Brunner HR, et al.
Prog Cardiovasc Dis 17:87-98, Sep-Oct 74 (59 ref.)

ANTICOAGULANTS

The pharmacodynamics of the oral anticoagulant drugs. O'Reilly RA.
Prog Hemostasis Thromb 2:175-213, 1974 (328 ref.)

AORTA

Intraaortic balloon counterpulsation. A review of physiological principles, clinical results, and device safety. Weber KT, et al.
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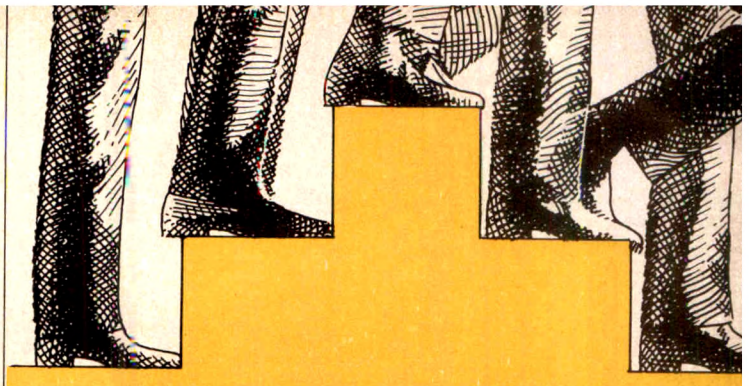

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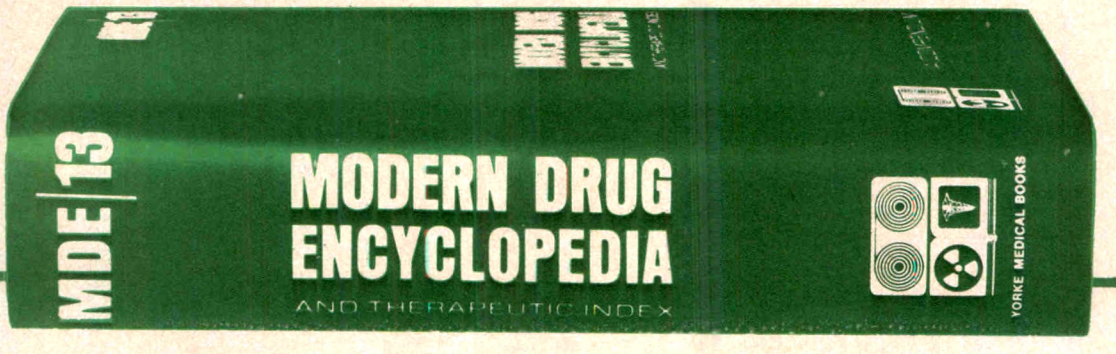

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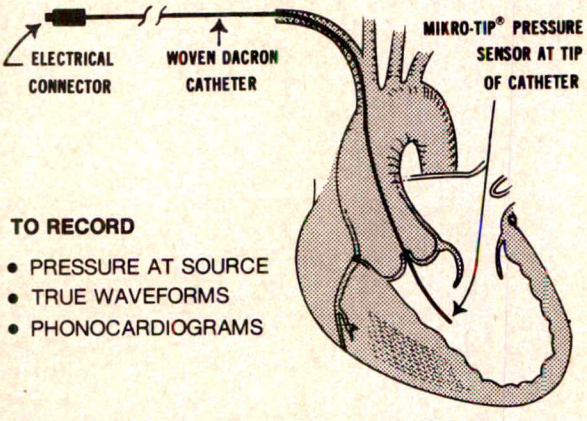

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Peritrate® SA Sustained Action
(pentaerythritol tetranitrate) 80mg

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.

For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

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Sustained Action
(pentaerythritol tetranitrate) 80 mg

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PE-GP-51

The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary.

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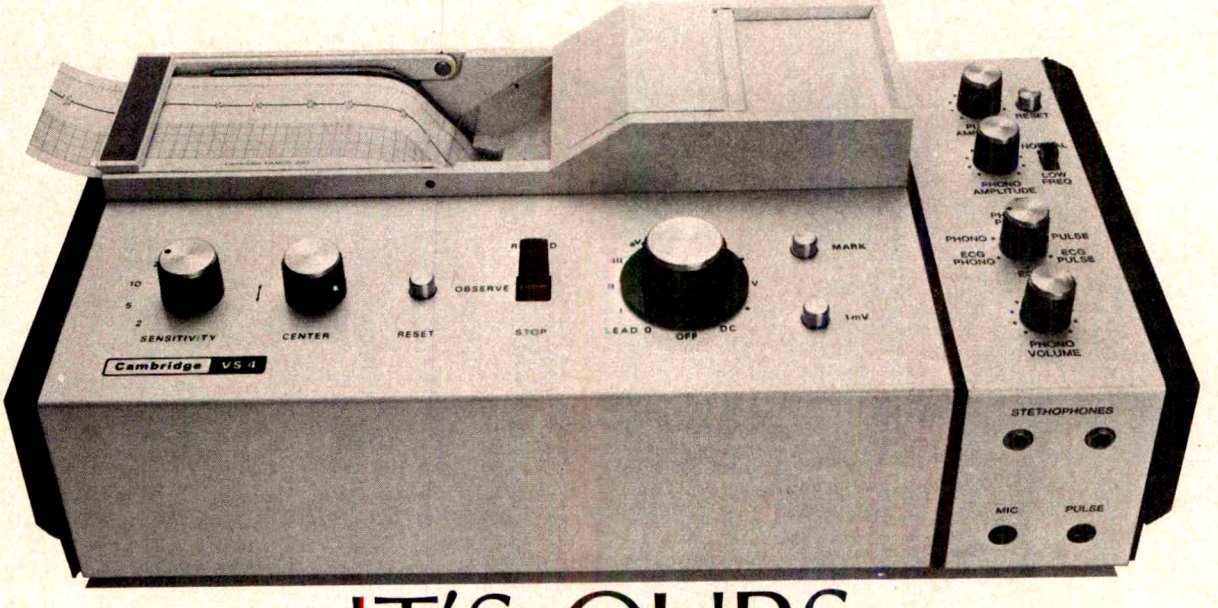

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You can order the VS-4 with the HS/PW Module installed at the factory, or your present VS-4 can be fitted with the Module by the Cambridge representative in your area. The conversion is simple, inexpensive and reliable.

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The newest Ekoline 20A® features multi-parameter capability.

Two new modules give the Smith Kline Instruments Ekoline 20A® an unmatched multi-trace capability. The Isolated Sweep/EKG Module and the Multi-Parameter Amplifier Module enable the E20A Ultrasonoscope to produce traces for ultrasound, EKG, phono and carotid pulse or apex. Combine this with the Fiber-optic Recorder and the result is high quality, grey scale strip chart recordings of pertinent information—at a surprisingly low cost.

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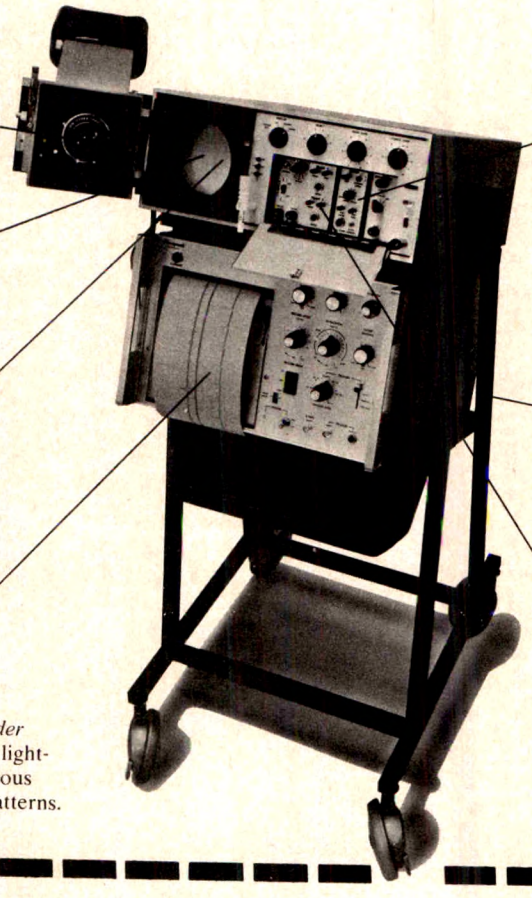
4. *New Fiber-Optic Line-Scan Recorder* utilizes fiber-optic CRT to expose light-sensitive paper, producing continuous "strip-chart" recordings of echo patterns.



5. *New Isolated Sweep/EKG System* Converts A-Mode echo display from a moving organ into M-Mode display. Features isolated, linear, and movable EKG.

6. *New Equipment Cart* conveniently houses 'Ekoline 20A' and Recorder. Permits complete system to be readily moved to any location throughout the hospital.

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Please:

☐ Have representative call me to arrange a demonstration.

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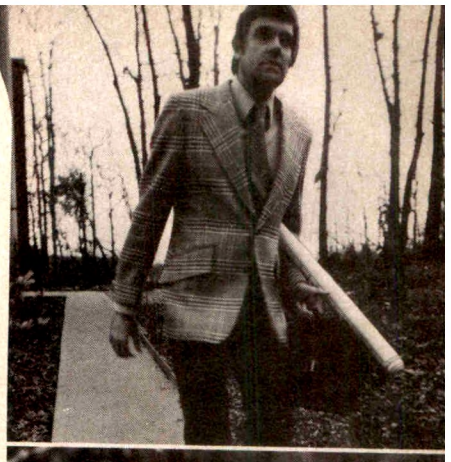
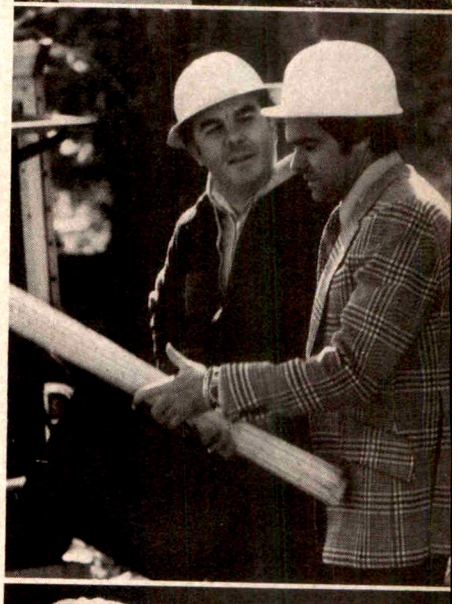
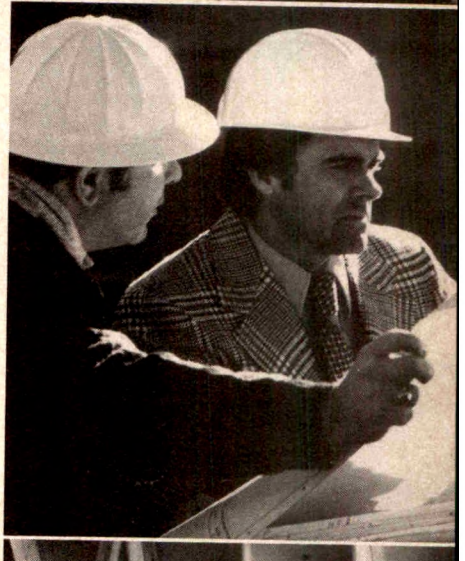
AN ANTIHYPERTENSIVE FROM AYERST

the "healthy" hypertensive







It may be years before he experiences a single symptom of hypertension. But left untreated, even mild to moderate elevations of blood pressure may quietly strip years from an otherwise healthy and active life. Early control with DIUCARDIN may help forestall damage to healthy target organs.

DIUCARDIN provides approximately the same diuretic potency as hydrochlorothiazide at maximal therapeutic dosage. With DIUCARDIN, the onset of diuresis is gradual and may be maintained for twelve hours or more with a single dose.[1,2] The antihypertensive effect of DIUCARDIN is usually maintained in long term use. For many patients on DIUCARDIN, a convenient once-a-day dosage may suffice.

DIUCARDIN provides a good beginning for many hypertensive patients. DIUCARDIN 50 mg. Tablets. For mild to moderate hypertension and adjunctive therapy for many types of edema.

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controlled early on

Diucardin® TABLETS

(hydroflumethiazide)

diuretic/antihypertensive

(See prescribing information on next page.)

For the "healthy" hypertensive, early control with

Diucardin® TABLETS (hydroflumethiazide)

diuretic/antihypertensive

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

The mechanism(s) of the antihypertensive action of the thiazides has not been elucidated.

INDICATIONS: **Hypertension:** DIUCARDIN alone may provide adequate control in mild or moderate hypertension. In severe hypertension or in cases of mild or moderate hypertension which do not respond adequately, DIUCARDIN may be used in conjunction with other antihypertensive agents.

DIUCARDIN alone or in conjunction with other antihypertensive agents is indicated for control of hypertension in pregnancy. (See WARNINGS)

Edema: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: **Gastrointestinal:** anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: **Usual adult dosage:** 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN—No. 702—Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.

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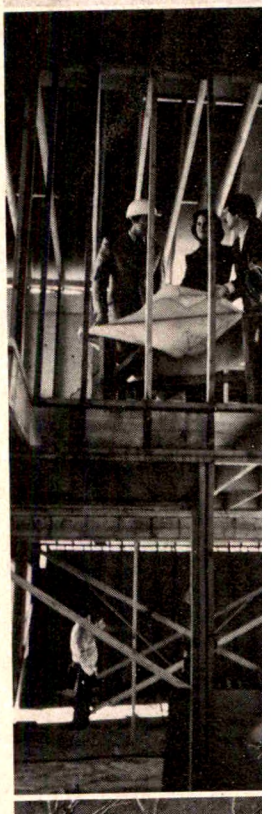

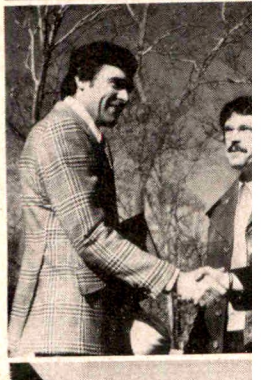

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The purpose of this monograph is to provide current information regarding the role of arrhythmias in ischemic heart disease and to highlight a number of laboratory and clinical experiences obtained with a new antiarrhythmic drug, 17-monochloroacetylajmaline, (MCAA).

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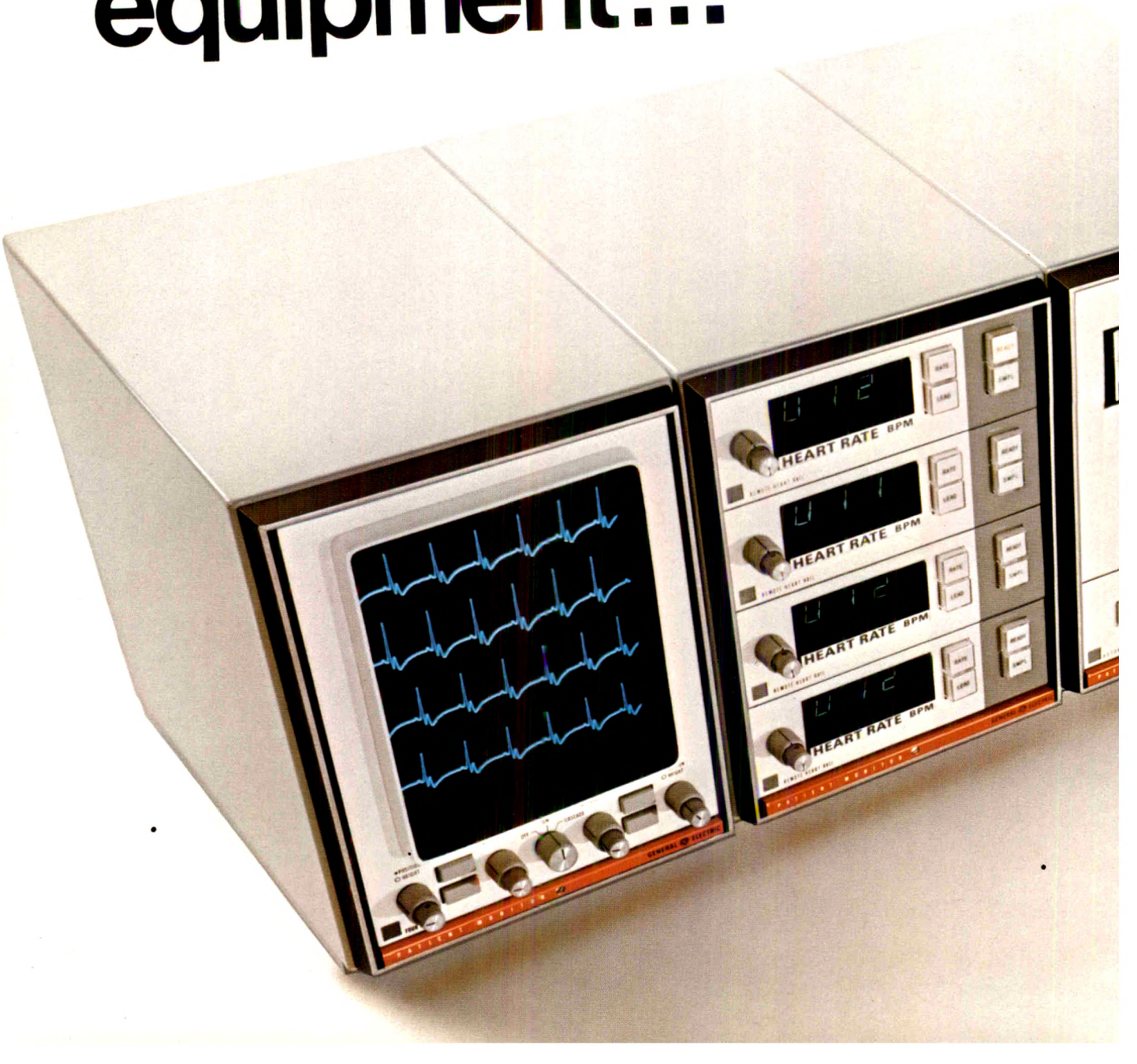

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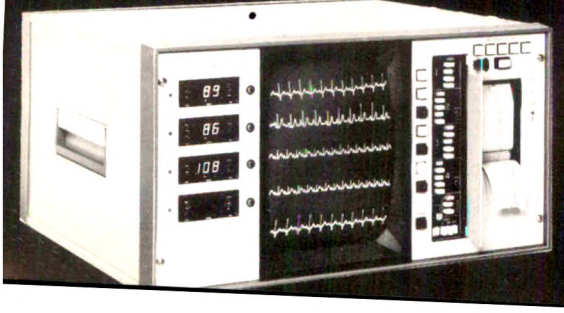

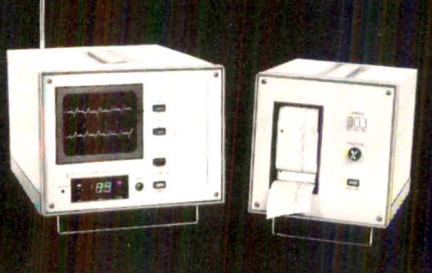

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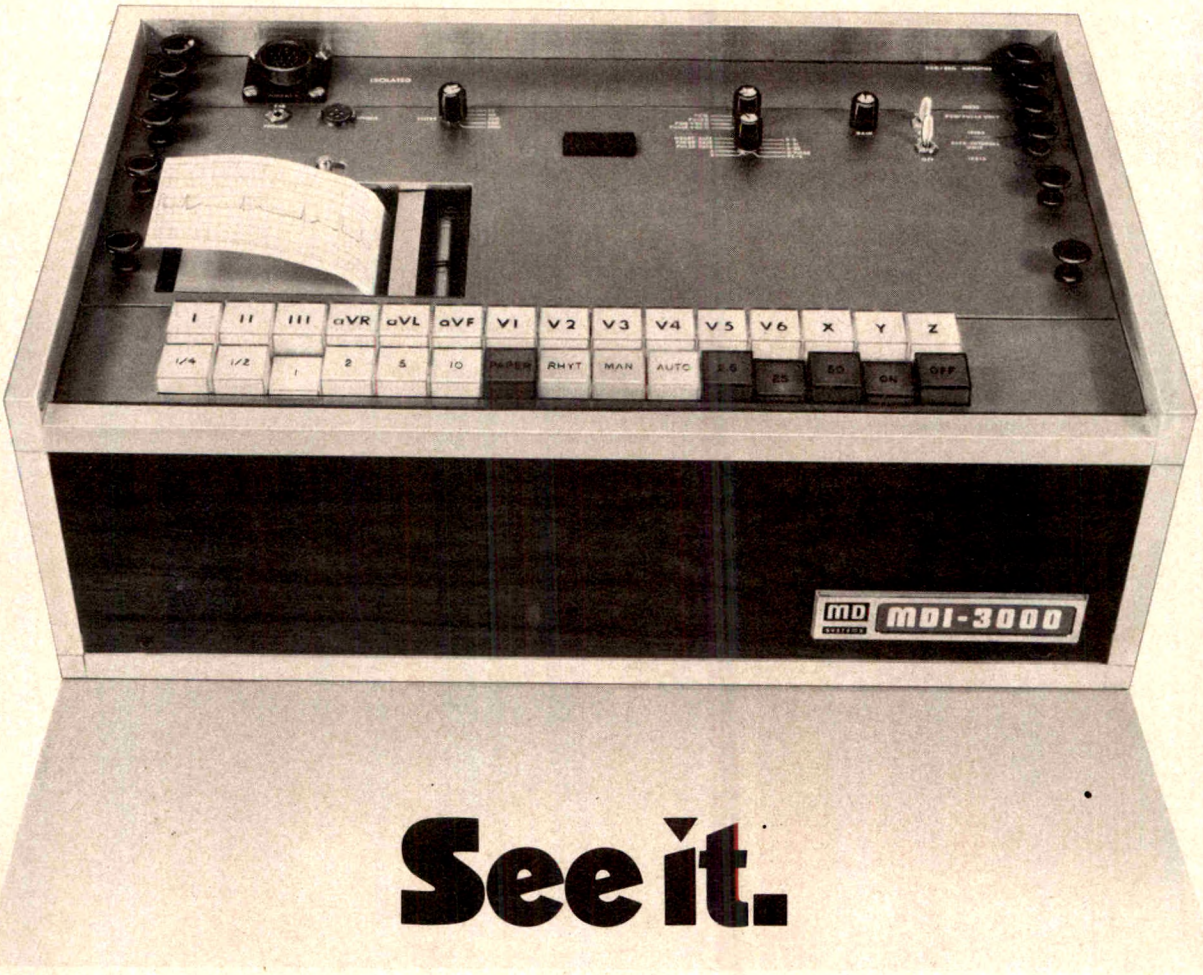

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* **INDICATIONS**

Based on a review of a related drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Sublingual "Probably" effective:
For the treatment of acute anginal attack and for prophylaxis in situations likely to provoke such attacks.

Oral "Possibly" effective:
For the relief of angina pectoris. It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Idiosyncrasy to this drug.

WARNINGS:
Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS:
Intraocular pressure is increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

ADVERSE REACTIONS:
Cutaneous vasodilation with flushing.
Headache is common and may be severe and persistent.
Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
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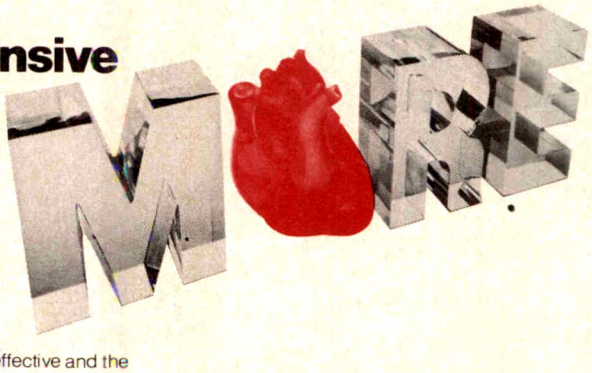

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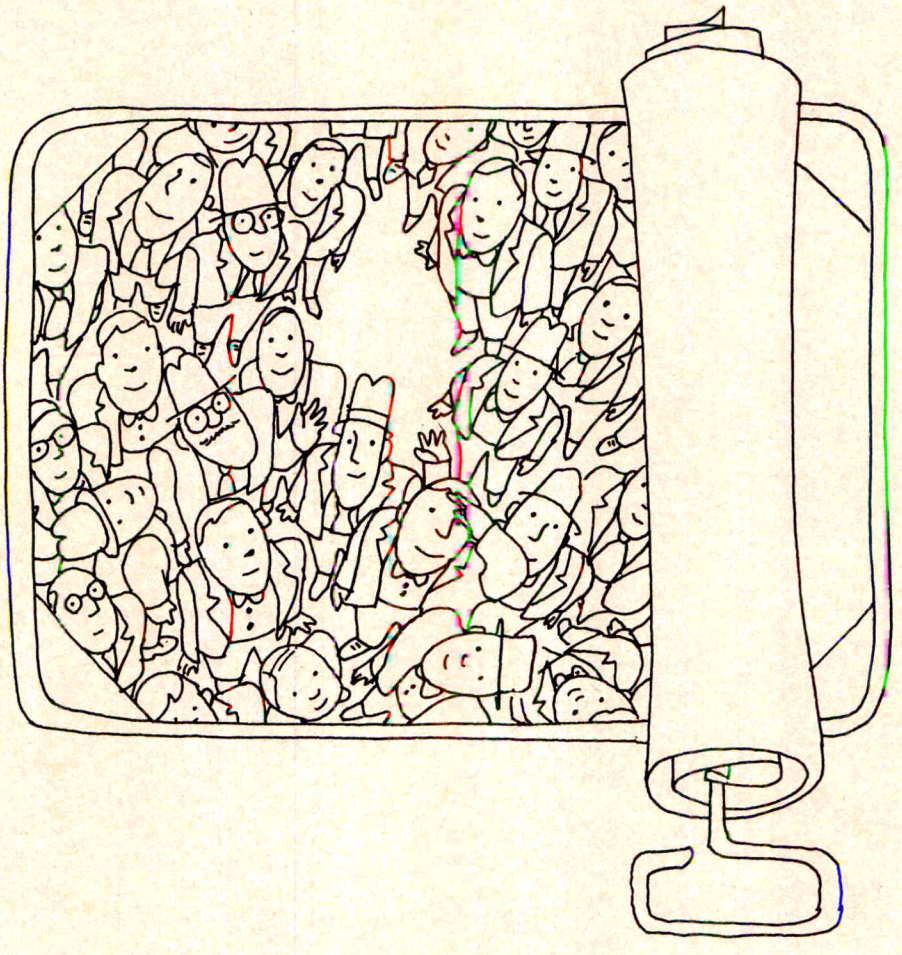

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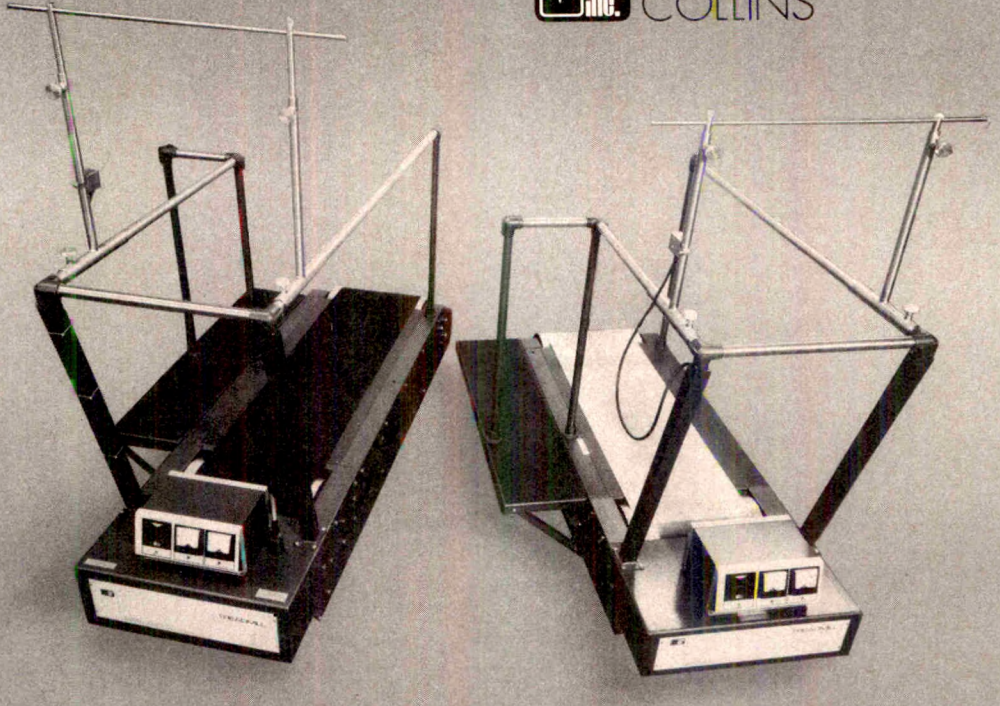

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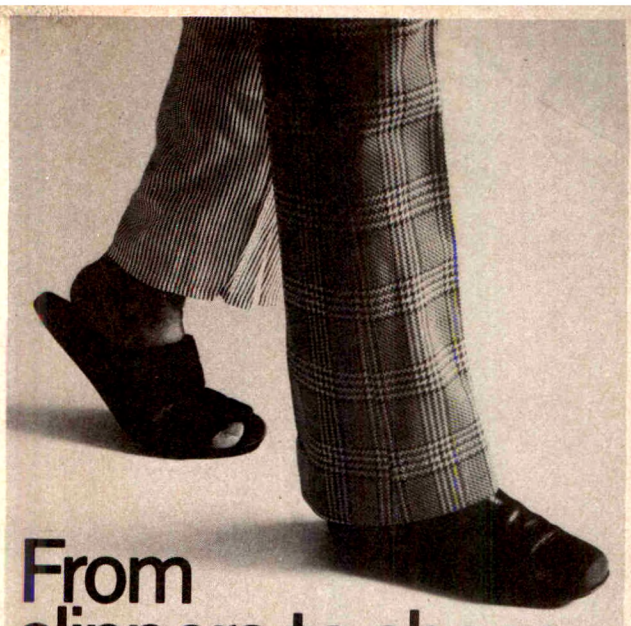

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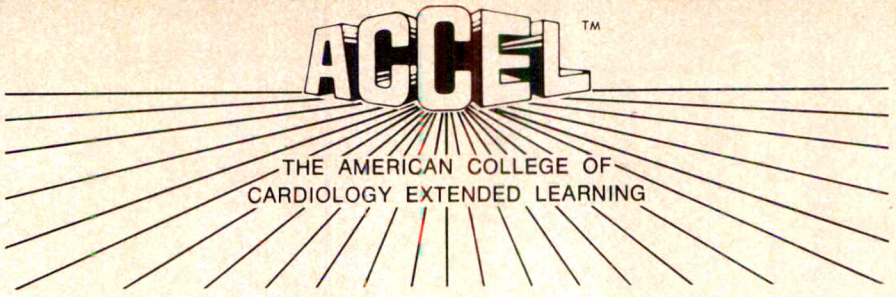

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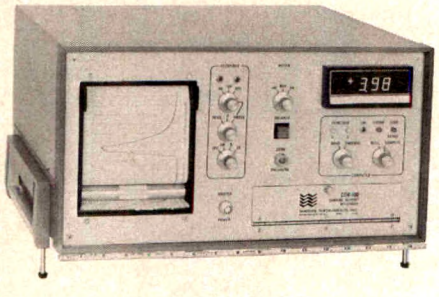

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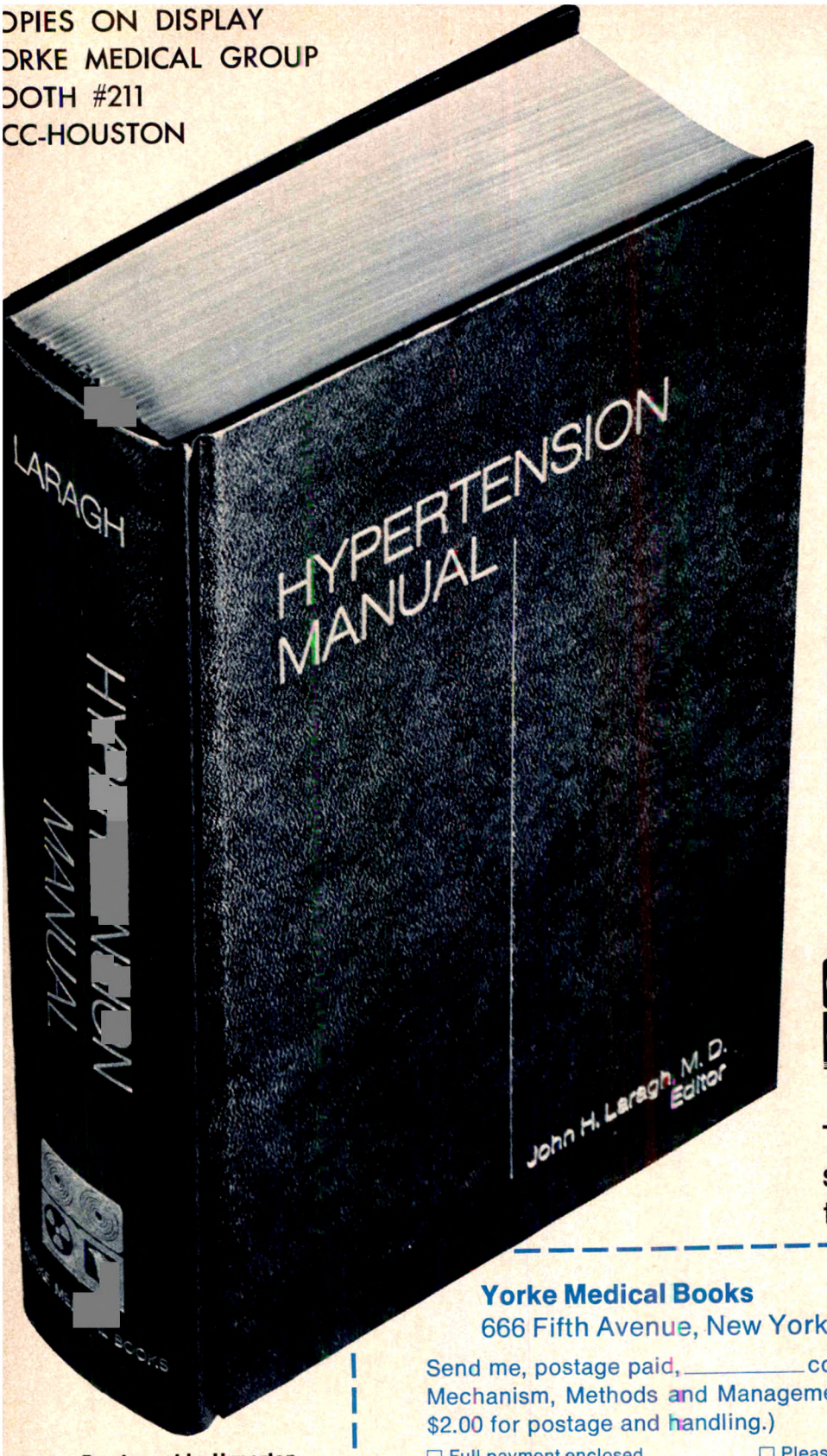

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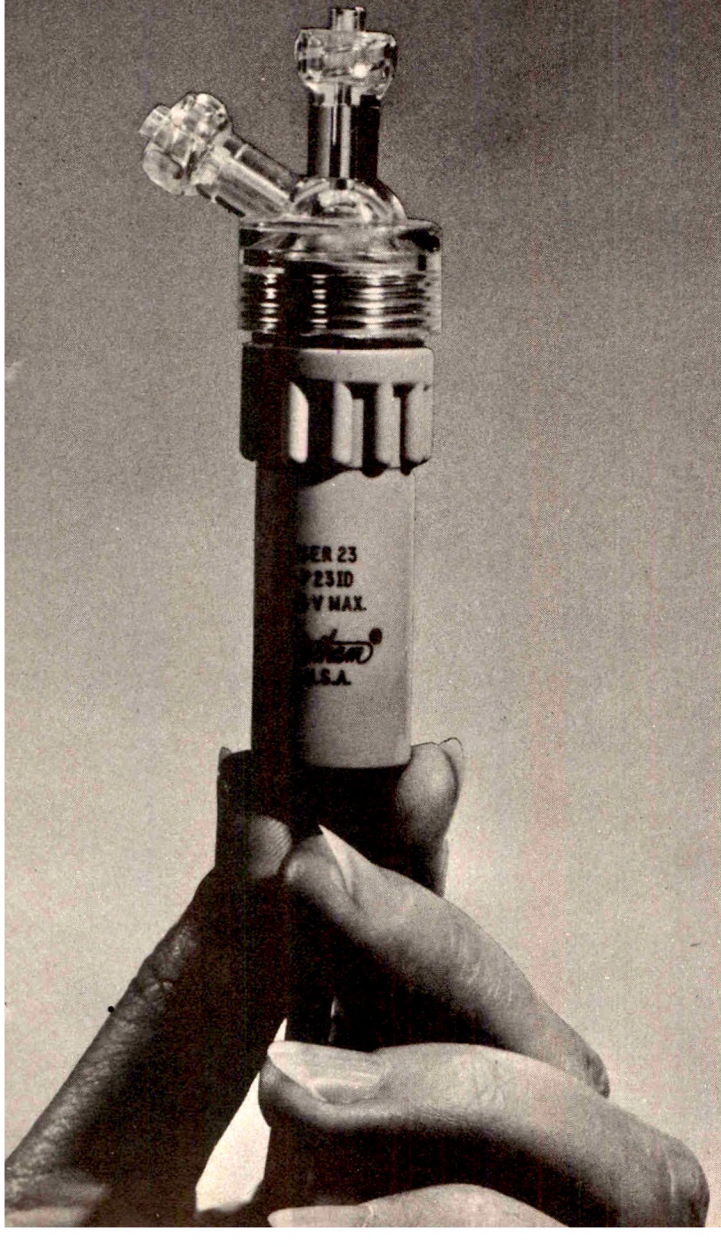

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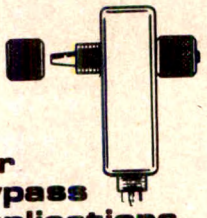

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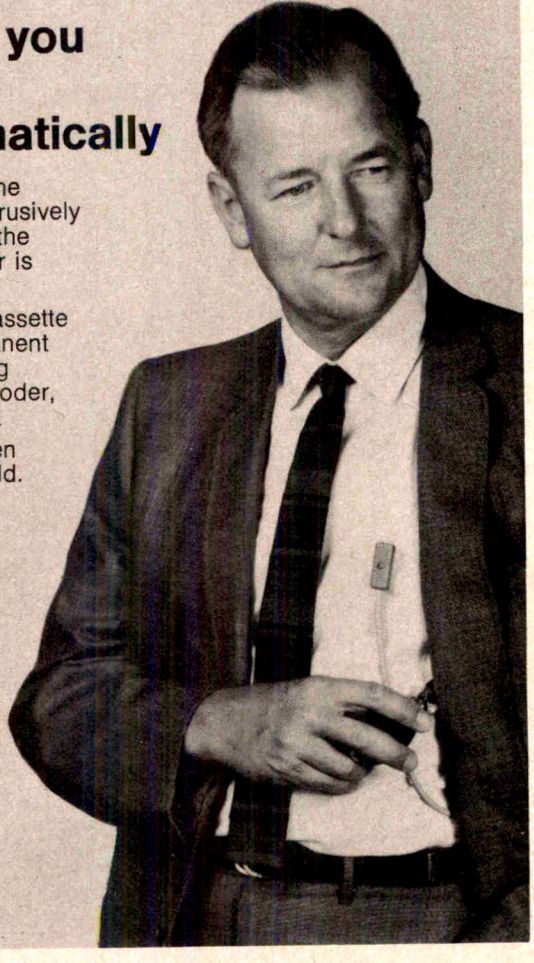

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Please send me complete details on the Remler Portable Blood Pressure Recorder System.

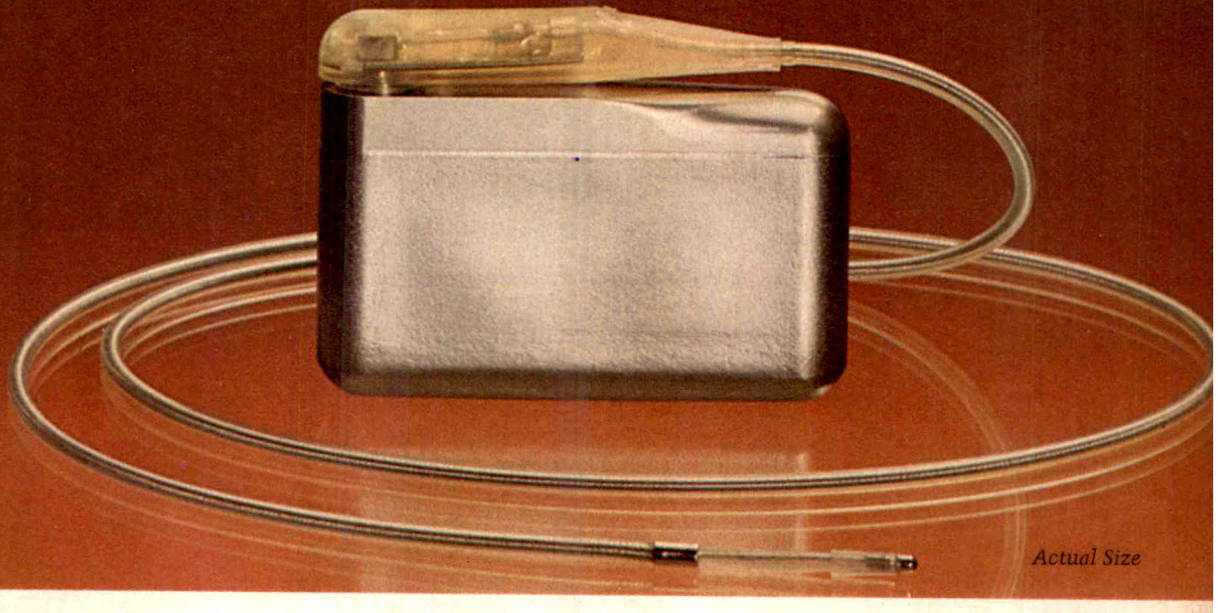
Name_____

Address_____

City/State/Zip_____

The rechargeable pacemaker.

Is it here to stay?



Actual Size

Since February, 1973, nearly 1000 Pacesetter™ rechargeable pacemakers* have been implanted without a single documented power source failure and only one electronic malfunction. About half as thick and a third the volume of other pacemakers, the Pacesetter system offers unprecedented longevity (a design life of 30 years), higher reliability and a simpler implantation procedure.

Yet the elapsed time since these implants has hardly been sufficient to establish in and of itself the performance of the Pacesetter system. *How long will this unique system function in the harsh environment of the body? What is the life of the Power Cell? How reliable are the electronics? How long will the lead last? And what assurance is there of the manufacturer's ability to stand behind the system?*

Six years of testing

The facts are that no other pacemaker has been so rigorously tested prior to its introduction. Since early 1969 Pacesetter Systems Inc. and Johns Hopkins University have collaborated on extensive *in vivo* testing, as well as normal and accelerated cycle programs.

For example, over 3000 power cells have been tested over this period including an original 50 which, in addition to five years of real time tests, have accumulated the equivalent of 35 years of operation in accelerated tests. The results: *Not one PSI™ cell meeting initial standards has degraded or failed. And none has varied from normal operating characteristics after initial stabilization.*

Reliability has been achieved in the electronics circuitry* by 100% environmental and performance testing of all critical components. To eliminate the intrusion of body fluids, the pulse generator is hermetically sealed. And, because of the long Power Cell life, each pacemaker can be subjected to months of continuous testing.

The coaxial, redundant-wire lead* matches the reliability and longevity of the pacemaker. Laboratory tests indicate a typical life more than ten times greater than other leads.

The portable AC charging console not only charges the pacemaker (providing eight weeks pacing with ample safety margin), but also receives and analyzes the pacemaker telemetry signal. The procedure is safe, simple, and assures the patient his pacemaker is functional.

Warranty

Pacesetter Systems Inc. (an associate of G. D. Searle & Co.) warrants the Pulse Generator and the Lead for *a full ten years.*

Complete documentation and clinical evidence is available for both Pacesetter asynchronous and demand models. We think the evidence is eminently clear:

The rechargeable pacemaker is indeed here to stay.

Pacesetter Systems, Inc.

An associate of G. D. Searle & Co.

12740 San Fernando Road, Sylmar, California 91342 (213) 367-1911

*Patents Pending

DYRENIUM®

brand of

triamterene 100 mg. capsules

Potassium-Sparing Adjunct to Congestive Heart Failure Therapy

1. Reduces risk of digitalis toxicity due to furosemide- or thiazide-induced excessive potassium excretion.

2. Provides additive diuretic effect to furosemide or thiazides when reduction of fluid volume is vital.

3. Permits substantial reduction of furosemide or thiazide dosage while preserving diuretic effect.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy.

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Dyrenium (triamterene, SK&F) and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.
Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 100 mg. capsules in bottles of 100; in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co., Carolina, P.R. 00630
Subsidiary of SmithKline Corporation

J.A. 15

FEBRUARY 1975

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Symposium on the Effects of Surgical Treatment on the Natural History of Acquired Heart Disease
Part II: Aortic and Mitral Valve Disease

Assessment of Ventricular Performance

Pathophysiology of Atrioventricular Block

Contents on Page A9

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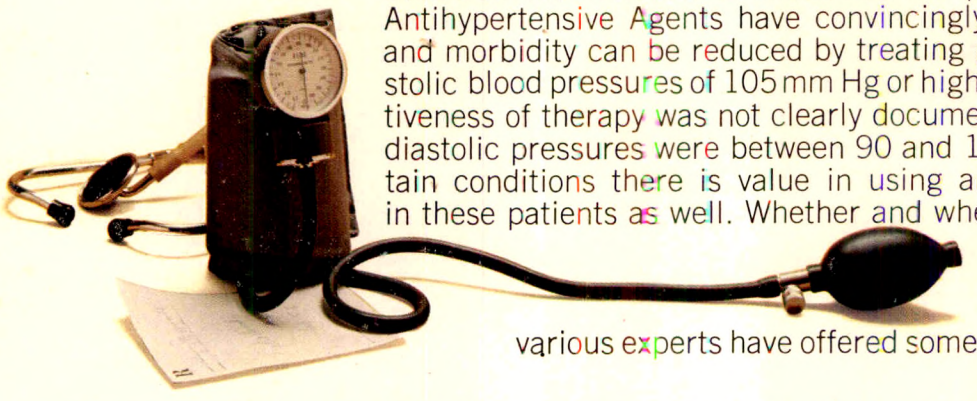
A YORKE MEDICAL JOURNAL

In the 90–104 mm Hg Diastolic Range—

When should medical management of hypertension include medication?

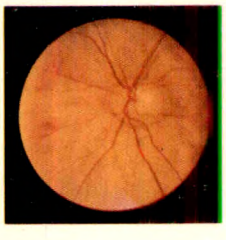


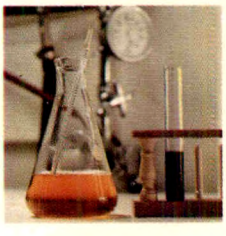
Data from the Veterans Administration Cooperative Study Group on Antihypertensive Agents have convincingly shown that mortality and morbidity can be reduced by treating patients with fixed diastolic blood pressures of 105 mm Hg or higher.[1] Although the effectiveness of therapy was not clearly documented in patients whose diastolic pressures were between 90 and 104 mm Hg, under certain conditions there is value in using antihypertensive agents in these patients as well. Whether and when to begin medication remains a matter of individual physician judgment. However, various experts have offered some useful guidelines.

Dr. Edward D. Freis, chairman of the VA Study Group, bases his decision on the following determining factors:[2]

Target Organ Damage

Such pathologic changes as retinopathy, left ventricular hypertrophy, and proteinuria are indications that hypertension is causing organic damage and should be treated immediately and aggressively.



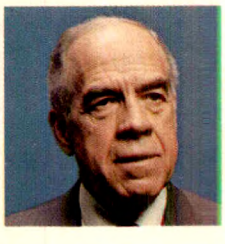


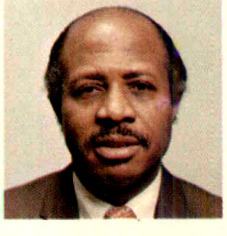
Diabetes or Hypercholesterolemia

These diseases tremendously increase the risk of coronary disease, even in patients with modest blood pressure elevations.

Sex

Men have a higher risk than women of developing the complications of hypertension.



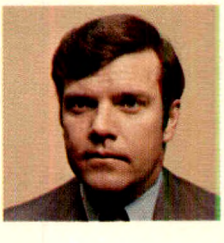


Race

Blacks tend to have earlier and more severe complications of hypertension than do whites.

Age

The younger the patient, the more hypertension will reduce his life expectancy.



Family History of Hypertension

If either parent had a major hypertensive complication, this adds significantly to the risk.

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg, JAMA *213*:1143, Aug 17, 1970.
2. Hypertension 1973: An expert draws the line on whom to treat, Patient Care 7:63, April 15, 1973.
3. Kirkendall WM: What's with hypertension these days? Consultant *11*:13, Jan 1971.
4. Finnerty FA Jr: How to treat arterial hypertension, American Family Physician 7:99, April 1973.

Kirkendall generally prefers to withhold medication when the sustained diastolic pressure is below 100 mm Hg unless "...a number of adverse factors exist, such as male sex, family history of vascular disease, youth, evidence of heart or kidney involvement."[3]

Finnerty finds it good practice to treat every patient whose diastolic pressure is persistently over 100 mm Hg. But he also says that "no definite statement can be made about the management of patients whose diastolic blood pressure averages between 90 and 100 mm Hg on repeated visits. If the patient is younger than 45 and there is a family history of hypertensive complications or the presence of end-organ damage (retina, heart, kidneys), treatment is probably indicated."[4]

When medical management includes medication: start with HydroDIURIL®

(HYDROCHLOROTHIAZIDE | MSD)

Once the decision to place patients on medication has been reached, many physicians choose to begin with a thiazide. HydroDIURIL is the first choice of many, because of their long years of experience with this antihypertensive. Patients whose therapy begins with HydroDIURIL frequently can continue to benefit from it for prolonged periods of time. For the adult patient, the usual starting dosage is 50 mg b.i.d. Dosage adjustments are recommended as the patient responds to treatment.

TABLETS, 25 mg and 50 mg

HydroDIURIL®

(HYDROCHLOROTHIAZIDE | MSD)

therapy to start with in hypertension

For a brief summary of prescribing information, please see following page.

addendum

MSD
MERCK SHARP & DOHME

"Required Reading" For Your Hypertensive Patients

Because of the importance of patient motivation, Merck Sharp & Dohme offers "High Blood Pressure," a concise, pocket-sized booklet that defines the patient's own role in the management of hypertension. This booklet is available for you to give to your patients. It is designed to reinforce your explanation of hypertension and it emphasizes the importance of patient understanding in adhering to the regimen you prescribe.

Please ask your Merck Sharp & Dohme Professional Representative or write Professional Service Department, West Point, Pa. 19486 for a supply of this booklet.

When medical management includes medication

HydroDIURIL®
(HYDROCHLOROTHIAZIDE | MSD)

therapy to start with in hypertension

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia and cumulative effects may develop. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; the effect of discontinuance of therapy on serum calcium and phosphorus levels may be helpful in assessing the need for parathyroid surgery in such patients.

When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

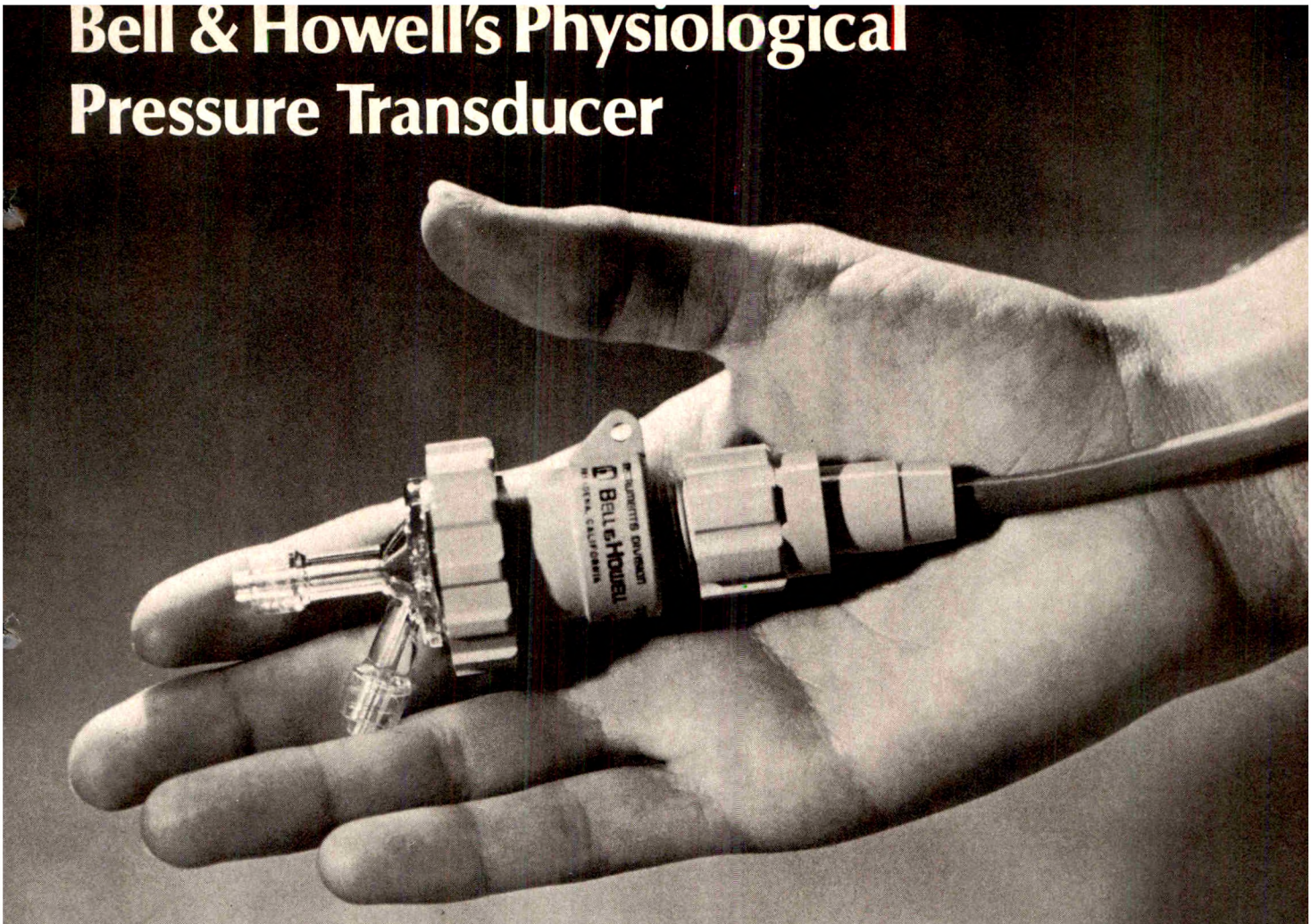
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD
MERCK SHARP & DOHME

Bell & Howell's Physiological Pressure Transducer



Safety...Accuracy...Tradition

For monitoring patient blood pressures, few instruments equal the levels of accuracy and safety provided by Bell & Howell's Model 4-327I Physiological Pressure Transducer.

Backed by more than 35 years experience in the development of quality, precision instrumentation, the Model 4-327I incorporates three levels of isolation to prevent the accidental introduction of electrical current.

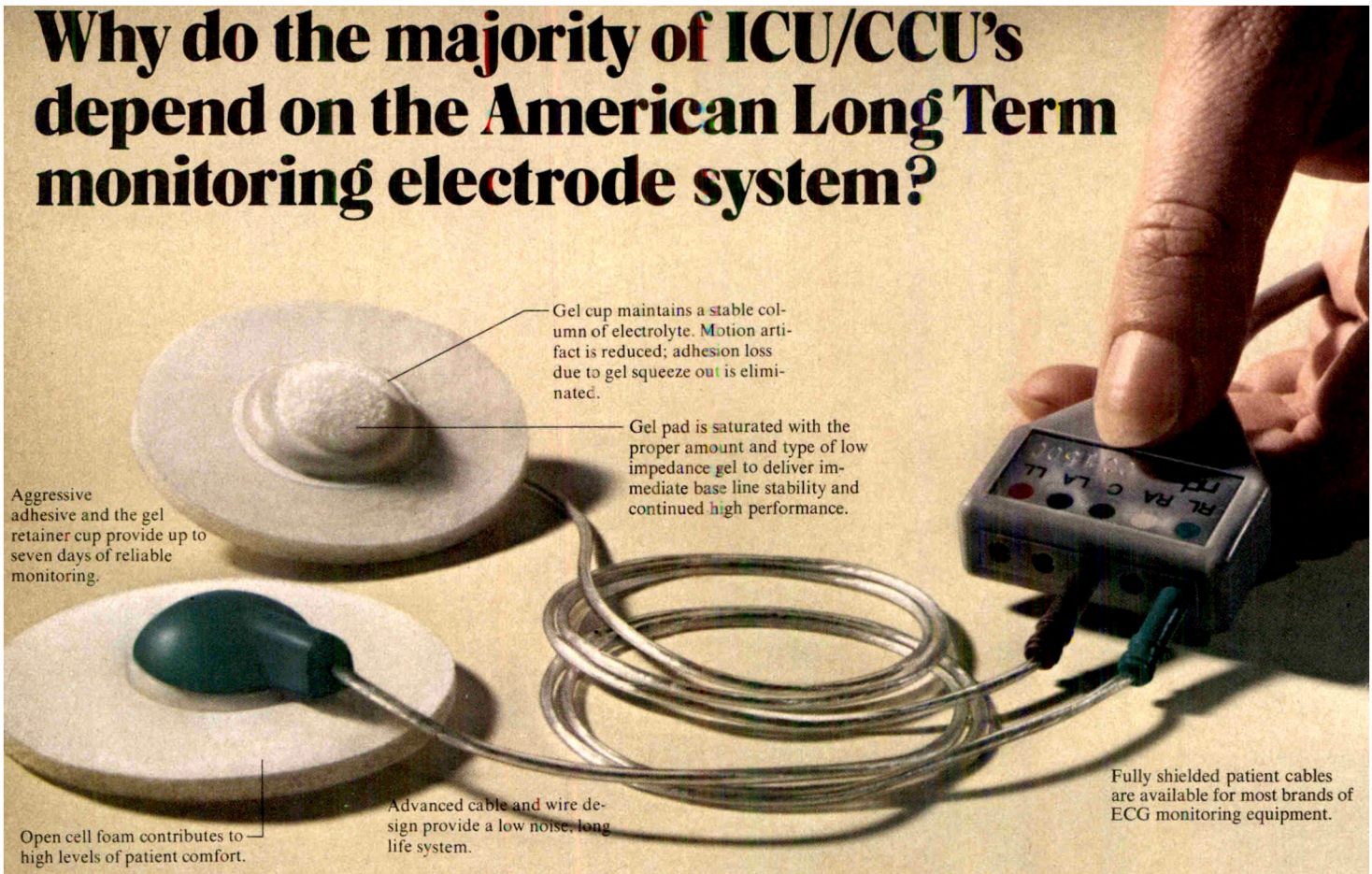
Ease of operation and practicality are built-in features. Cables can be interchanged to operate with any existing monitoring system. The Model 4-327I cannot be damaged by defibrillation or electrocautery equipment usage. Other features of the Model 4-327I include replaceable dome and body, rugged construction and precalibration.

To find out more about the Model 4-327I, write us at 360 Sierra Madre Villa, Pasadena, California 91109.

CEC/INSTRUMENTS DIVISION

BELL & HOWELL

Why do the majority of ICU/CCU's depend on the American Long Term monitoring electrode system?



This is the system that has established new standards for high performance in long term ECG monitoring.

Designed for single patient use, the self-adhering silver/silver chloride electrode is pregelled with the correct amount of proper electrolyte. Adhesion loss and electrolyte evaporation are virtually eliminated by the gel retaining cup. The results: Immediate base line stability and better long term performance than any other electrode —reusable or disposable—is capable of delivering.

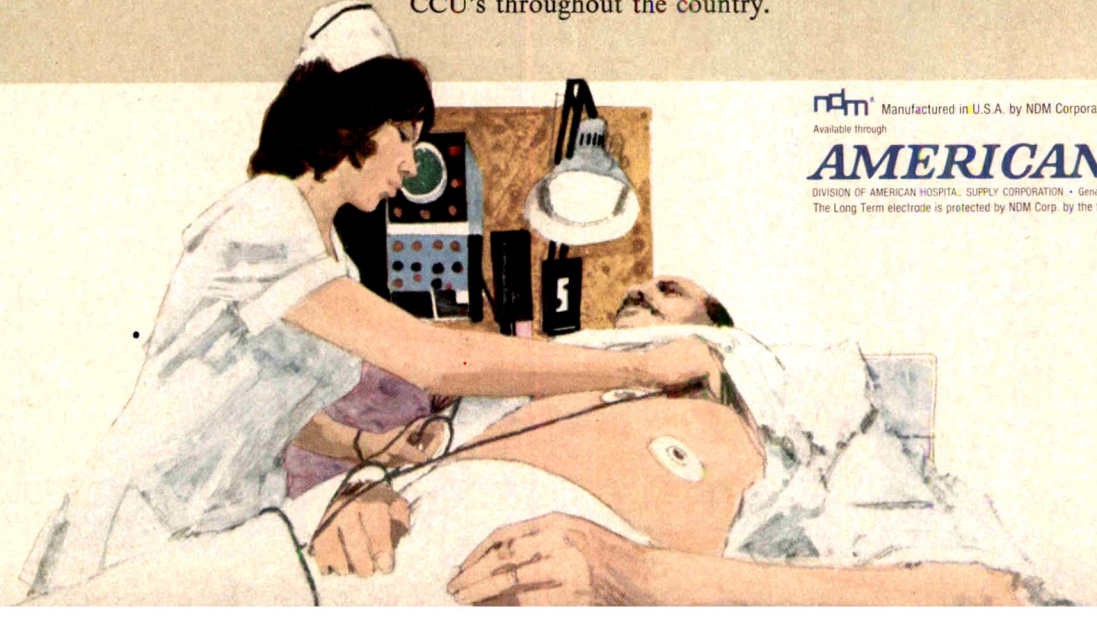
Open cell foam complements the electrode's mild gel formulation and low profile to enhance patient comfort. When used as directed, American's Long Term Electrode provides from five to seven days of continuous, accurate monitoring . . . with no discomfort to the patient.

This advanced electrode, used with the appropriate American leadwire and cable, is fully compatible with your present ECG equipment.

A clinical trial will show you why the American Long Term Electrode system is the overwhelming choice of ICU/CCU's throughout the country.

Please contact your American Hospital Supply or NDM representative and ask for:

- A demonstration of the system's benefits.
- A no obligation clinical trial. American will supply electrodes, leadwires and cables to adapt to your present monitoring equipment during the trial period.
- A total inservice for your staff.
- Information about our nationwide technical support program.



ndm® Manufactured in U.S.A. by NDM Corporation, Dayton, Ohio 45439

Available through

AMERICAN HOSPITAL SUPPLY

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The Long Term electrode is protected by NDM Corp. by the following U.S. Patents: 3,696,807; 3,701,346; 3,713,435.

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120
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KEEP THE HYPERTENSIVE PATIENT ON THERAPY

KEEP THERAPY SIMPLE WITH

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Just 'Dyazide' once daily or twice daily
No inconvenient potassium supplements
Nor special K^+ rich diets needed as a rule

Two prime reasons patients drop out of hypertensive therapy are (1) the patient failed to understand directions, and (2) the regimen was overly complicated. Dosage is simple with 'Dyazide', easily understood, once or twice daily, depending on response. There's no need to complicate the regimen with potassium supplements or unwieldy potassium-rich diets.

'Dyazide' can occasionally cause hyperkalemia. Serum potassium and BUN should be checked during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetic patients). If hyperkalemia develops, 'Dyazide' should be withdrawn and a thiazide alone substituted.

The Dyrenium® (triamterene, SK&F) component of 'Dyazide' conserves potassium. Therefore, dietary potassium supplements or potassium salts should not be used with 'Dyazide' unless hypokalemia develops or dietary intake of potassium is markedly impaired.

Use 'Dyazide' with caution during pregnancy or in women who might bear children; potential benefits should be weighed against possible hazards to the fetus.

See next page for indications and brief summary of prescribing information.

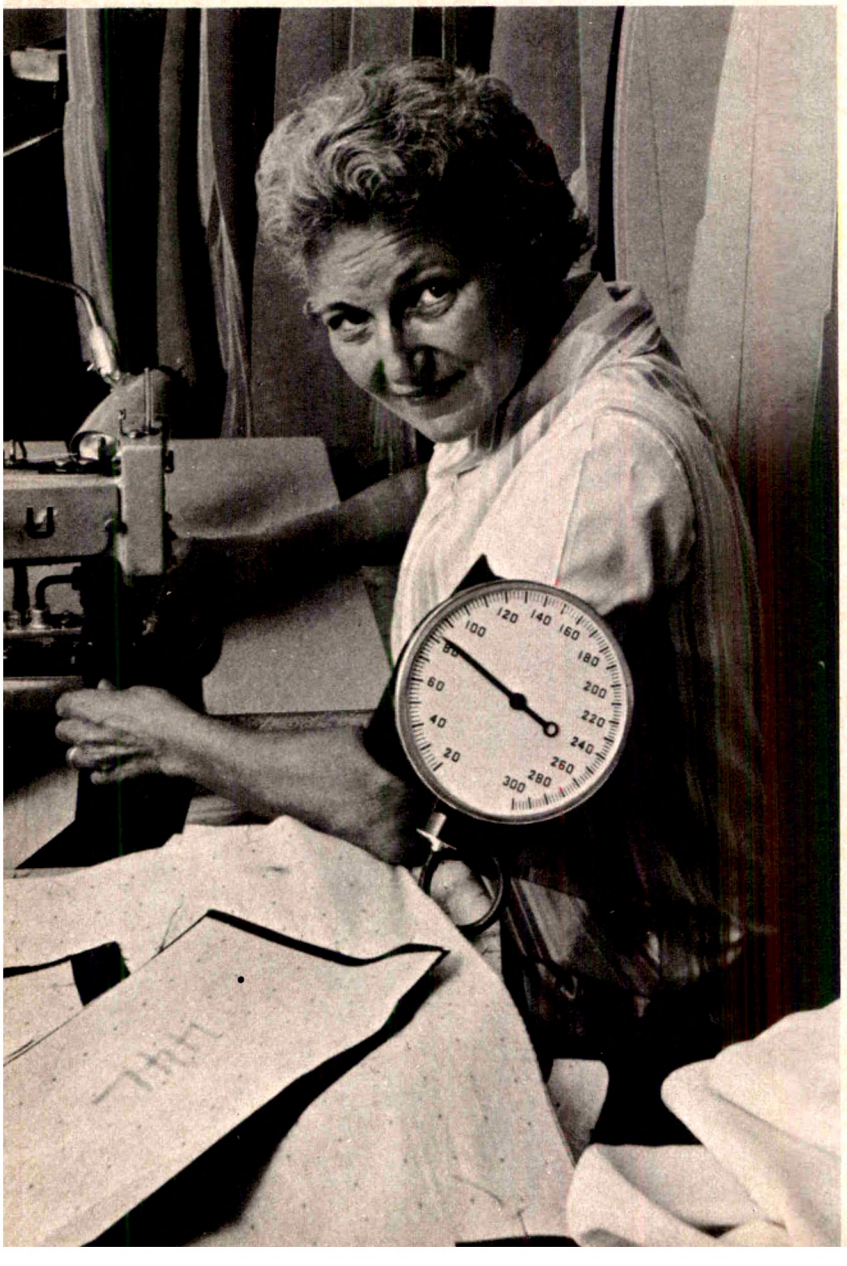
DYAZIDE®

TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP

KEEP THERAPY SIMPLE WITH DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP



Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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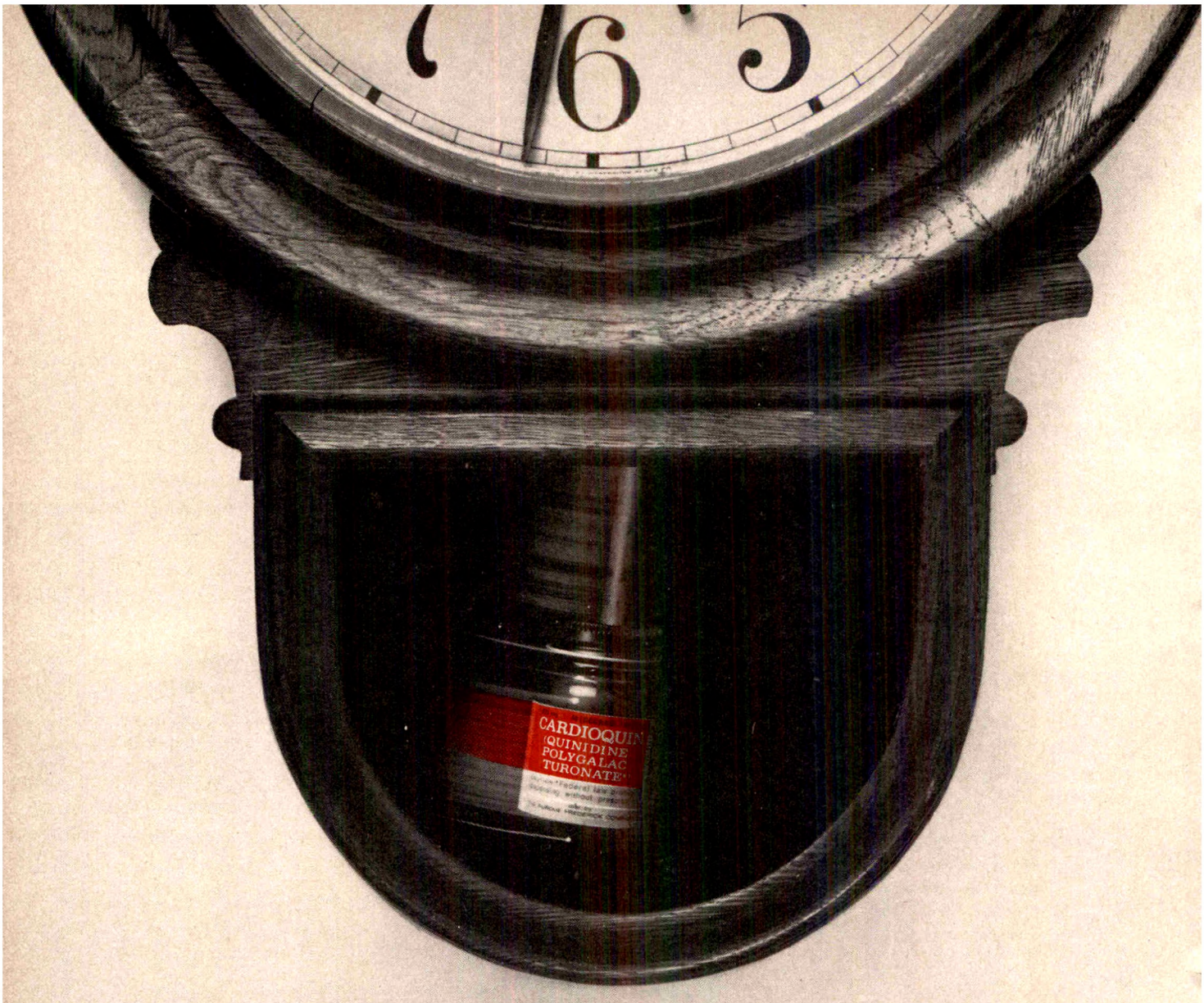

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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199 Atrioventricular and Intraventricular Conduction in Hyperkalemia

TALI BASHOUR, IRENE HSU, H. JOEL GORFINKEL, RAJASEKARAN WICKRAMESEKARAN and JORGE C. RIOS

As shown in 12 patients, hyperkalemia often produces conduction disturbances in the specialized intraventricular conduction system and electrocardiographic patterns of fascicular block. His bundle recording and atrial pacing in one patient demonstrated intraatrial conduction delay and markedly prolonged conduction time in the His-Purkinje system.

204 Blood Platelet Response to Plasma from Patients with Ischemic Heart Disease

IRWIN J. SCHATZ and IRWIN GROSS

This electron microscopic study found increased spread platelet forms in 14 patients with acute and chronic ischemic heart disease compared with findings in 14 asymptomatic control subjects. When platelets from these 14 control subjects were exposed to plasma from the patients with ischemic heart disease, spread forms increased from 13.4 ± 9.1 to 44.5 ± 15.5 percent. There appears to be a factor in the plasma of patients with ischemic heart disease that causes normal platelets to become spread and that is unrelated to hormonal and therapeutic influences.

211 Coronary Arteriographic Findings in 1,000 Women Under Age 50

C. CHARLES WELCH, WILLIAM L. PROUDFIT and WILLIAM C. SHELDON

In 1,000 women under age 50 examined by coronary cinearteriography because of chest pain, only half of those thought to have angina pectoris had significant coronary artery disease. At least 50 percent narrowing of one or more coronary arteries was found in 236 patients. Electrocardiographic evidence of myocardial infarction was uncommon in women with single vessel disease. Coronary arteriography is recommended before diagnosing coronry artery disease in young women with angina-like pain.

216 Radiation-Related Pericarditis

ROBERT G. MARTIN, JOHN C. RUCKDESCHEL, PAUL CHANG, ROGER BYHARDT, RICHARD J. BOUCHARD and PETER H. WIERNIK

Pericardial effusion developed in 29.6 percent of 81 patients with Hodgkin's disease who received radiation therapy. Five required partial pericardiectomy for cardiac tamponade, without evidence of recurrent Hodgkin's disease.

Continued on page A13

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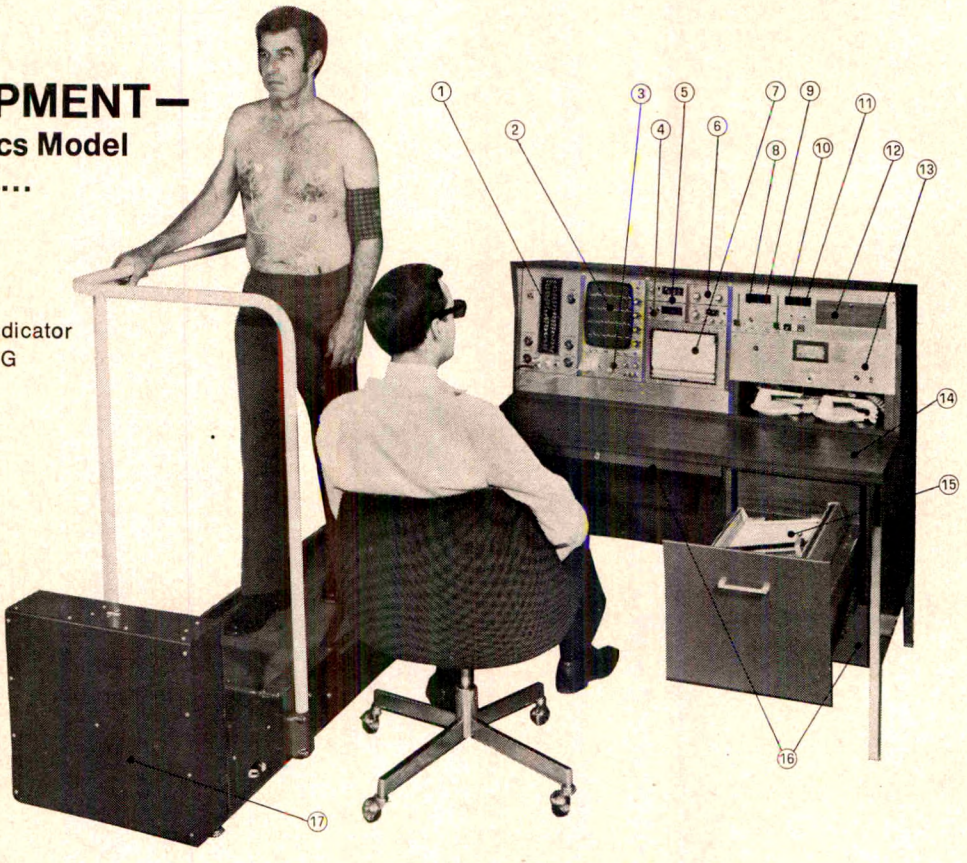

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221 Natural History of Aortic and Mitral Valve Disease

ELLIOT RAPAPORT

Stenotic lesions have a poorer prognosis than chronic regurgitant lesions and generally need earlier surgical intervention. However, acute valvular insufficiency is poorly tolerated and may require emergency surgery. An appreciation of the natural history is necessary for assessment of patients for surgery and for evaluation of surgical results.

228 Long-Term Follow-Up of Isolated Replacement of the Aortic or Mitral Valve with the Starr-Edwards Prosthesis

DONALD A. BARNHORST, HERBERT A. OXMAN, DANIEL C. CONNOLLY, JAMES R. PLUTH, GORDON K. DANIELSON, ROBERT B. WALLACE and DWIGHT C. McGOON

Isolated replacement of the aortic or mitral valve by a Starr-Edwards prosthesis in 1,684 cases improved life expectancy over that of the natural history of valvular heart disease. Adequate anticoagulation, earlier performance of valve replacement and more complete repair of valvular dysfunction may increase survival rates.

234 Influence of Surgery on the Natural History of Rheumatic Mitral and Aortic Valve Disease

SIMON MUÑOZ, JOSE GALLARDO, JOSE R. DIAZ-GORRIN and OMAR MEDINA

In this large well controlled study, surgical treatment of 210 patients with rheumatic mitral or aortic valve disease proved clearly superior to medical treatment of 200 patients with similar disease. Mitral valvulotomy exerted the most positive effect in reducing mortality, showing a 5 year survival rate of 85 percent. The initial operative mortality mainly determined the 5 year survival rate. Survivors of cardiac surgery manifested appreciable improvement in cardiac function and reduced incidence of heart failure and atrial fibrillation.

EXPERIMENTAL STUDIES

243 Effects of Alcohol on Cardiovascular Performance After Experimental Nonpenetrating Chest Trauma

A. JAMES LIEDTKE and WILLIAM E. DeMUTH

The administration of alcohol can catastrophically reduce mechanical performance of the heart, producing transient and major arrhythmias and acute reductions in aortic pressure and cardiac index, in the presence of otherwise nonfatal cardiac injury secondary to nonpenetrating chest trauma in dogs.

251 Effects of Myocardial Hypoxia and Ischemia on Myocardial Scintigraphy

NORMAN I. LEVENSON, ROBERT J. ADOLPH, DONALD W. ROMHILT, MARJORIE GABEL, VINCENT J. SODD and LEON S. AUGUST

Although cesium-129 is useful for identifying myocardial infarcts it cannot be used to visualize transient exercise-induced regional myocardial ischemia, probably because of the delayed uptake of this agent by the myocardium. Scintigraphic studies may overestimate the size of an acute myocardial infarct in man by including the ischemic zone surrounding the infarct.

Continued on page A15

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METHODS

258 Ventricular Performance in Patients Based Upon Rate of Change of Power During Isovolumic Contraction

PAUL D. STEIN and HANI N. SABBAH

In 17 patients with angina pectoris who underwent diagnostic cardiac catheterization, the peak isovolumic rate of change of power (acceleration of energy transfer) in those with normal left ventricular performance was 31,000 ± 3,000 dynes cm sec^{-2} and in those with poor ventricular performance was 18,000 ± 2,000 dynes cm sec^{-2}. The data suggest that this determination may be a useful and sensitive indicator of ventricular performance in patients with coronary artery disease.

264 Isovolumic Fractional Rate of Change of Power: Its Applicability to Assessment of Ventricular Performance in Patients

PAUL D. STEIN and HANI N. SABBAH

The ratio of the instantaneous isovolumic rate of change of power describes meaningfully and usefully the capability of the ventricle to sustain during isovolumic contraction an acceleration of energy production relative to instantaneous rates of energy production. In this study the ratio distinguished between patients with normal and abnormal ventricular performance, thus indicating that it is a useful hemodynamic expression.

PEDIATRIC CARDIOLOGY

271 Solitary Interruption of the Arch of the Aorta. Clinicopathologic Review of Eight Cases

M. RENATE DISCHE, MARY TSAI and HAROLD A. BALTAXE

When total interruption or atresia of the aortic arch is not accompanied by other malformations, survival time is prolonged and the prognosis is improved, as shown in these reported cases. Ages at the time of diagnosis ranged from 8 to 56 years. Ascending and descending aortography helps to make the correct diagnosis. The lesions can be successfully repaired by direct anastomosis or by interposition of a graft between the proximal and distal aortic stumps.

278 Electrocardiographic Evidence of Left Ventricular Hypertrophy in Otherwise Normal Children. Clarification by Echocardiography

JOEL MORGANROTH, BARRY J. MARON, L. JEROME KROVETZ, WALTER L. HENRY and STEPHEN E. EPSTEIN

Normal echocardiographic values for left ventricular wall thickness, cavity dimensions and wall mass in 11 children apparently normal except for greatly increased precordial QRS voltage suggesting left ventricular hypertrophy indicate the value of echocardiography in determining the significance of such abnormal electrocardiograms. Increased precordial QRS voltage in children and adolescents, in the absence of other abnormalities, is an unreliable indicator of left ventricular hypertrophy.

REPORTS ON THERAPY

282 Electrophysiologic Effects of the Antiarrhythmic Agent Disopyramide Phosphate

BENJAMIN BEFELER, AGUSTIN CASTELLANOS, Jr., DAVID E. WELLS, M. CELESTE VAGUEIRO and BILLY K. YEH

Disopyramide phosphate given intravenously to 10 patients with cardiac disease shortened sinus recovery time, tended to reduce atrial refractoriness and prolonged the functional refractory period of the atrioventricular node. The mechanism of its antiarrhythmic action is similar to that of quinidine. The drug may be useful in arrhythmias associated with slow sinus rates.

Continued on page A17

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288 Concealed His Bundle Extrasystoles in Congenital Heart Disease

ANTOINE T. NASRALLAH, PAUL C. GILLETTE, CHARLES E. MULLINS, MICHAEL R. NIHILL and DAN G. McNAMARA

Concealed conduction of His bundle extrasystoles into the atrioventricular (A-V) junction caused them to mimick atrial nonconducted bigeminal rhythms in the surface electrocardiogram of one child and to simulate second degree A-V block and conducted junctional extrasystoles in the other child's tracing. His bundle recordings are safe and indispensable for correct diagnosis and treatment of conduction and rhythm disturbances even in the presence of complex congenital heart disease.

293 Electrocardiographic Manifestations of Dual Pathways of Retrograde Impulse Conduction in the Human Heart

YIGAL NOY and PETER FLEISCHMANN

Electrocardiographic data from three patients support the concept of two separate pathways for retrograde impulse conduction between the ventricles and atria.

CASE REPORTS

299 Conduction System in Systemic Lupus Erythematosus with Atrioventricular Block

SAROJA BHARATI, DOMINGO J. de la FUENTE, RONALD J. KALLEN, YASER FREIJ and MAURICE LEV

Granulation tissue replaced almost completely the sinoatrial and atrioventricular nodes in a 12 year old girl with fatal systemic lupus erythematosus, complete heart block, renal failure and hyperkalemia.

305 Systemic Lupus Erythematosus as a Cause of Severe Mitral Regurgitation. New Problem in an Old Disease

BERNADINE H. BULKLEY and WILLIAM C. ROBERTS

Healing of Libman-Sacks endocarditis treated with corticosteroid drugs caused severe mitral regurgitation in three patients with systemic lupus erythematosus, leading to death in two and necessitating mitral valve replacement in the third.

309 Myocardial Infarction Due to Coronary Atherosclerosis in Three Young Adults with Systemic Lupus Erythematosus

JOSE MELLER, CESAR A. CONDE, LUDWIG M. DEPPISCH, EPHRAIM DONOSO and SIMON DACK

The finding of coronary atherosclerosis at the postmortem examination in one of three young adults with lupus erythematosus and acute myocardial infarction suggests a more than coincidental relation between these two diseases. The other two survivors could have either coronary atherosclerosis or arteritis and there is no way to differentiate clinically between these lesions.

Continued on page A19

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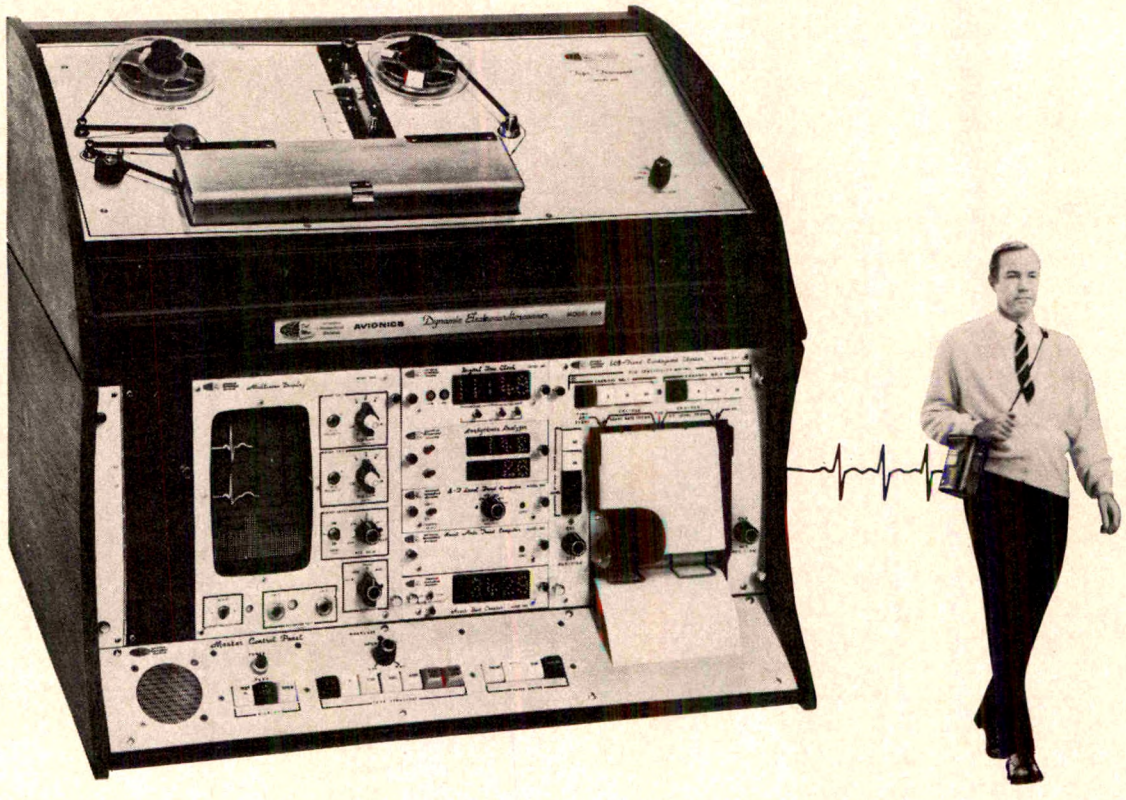

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315 **Bilateral Arteriosclerotic Coronary Arterial Aneurysms Successfully Treated with Saphenous Vein Bypass Grafting**

CHARLES S. WILSON, WALT F. WEAVER and ALAN D. FORKER

Aortocoronary saphenous vein graft surgery was performed successfully in a 48 year old laborer with bilateral arteriosclerotic coronary arterial aneurysms diagnosed preoperatively after a subendocardial infarction. In retrospect, ligation of the distal end of the aneurysm, not done in this patient, appears preferable to prevent recurrent embolization from the aneurysm into the distal grafted segment.

319 **Bilateral Nonfistulous Congenital Arterial Aneurysms**

CHARLES S. WILSON, WALT F. WEAVER, E. D. ZEMAN and ALAN D. FORKER

Premortem clinical features—chest pain, systolic and diastolic murmurs and an expanding mass on the right heart border in the chest film—were overlooked clues to bilateral congenital coronary arterial aneurysms found at postmortem in a 15 year old boy who died after playing basketball.

324 **Aortic Origin of the Left Pulmonary Artery. Variant of Tetralogy of Fallot**

ERWIN ROBIN, BORIS SILBERBERG, SUNILENDU N. GANGULY and KONSTANTINOS MAGNISALIS

This 5 month old child with tetralogy of Fallot associated with aortic origin of the left pulmonary artery and hypoplasia of the left main artery and presenting with stunted growth, cyanosis, a continuous murmur over the pulmonary area and a hypervascular left lung on chest X-ray examination required cardiac catheterization and angiocardiography for final diagnosis. Recognition of the anomalous origin of the left pulmonary artery is essential before surgery is attempted, preferably at an early age.

EDITORIALS

330 **Prevention of Heart Disease by Control of Risk Factors: The Time Has Come to Face the Facts**

ELIOT CORDAY and STEPHEN RICHARD CORDAY

SPECIAL DEPARTMENTS

334 **American College of Cardiology News**

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The place of INDERAL (propranolol hydrochloride) among the standard drugs for the treatment of disturbed cardiac rhythm has been frequently reaffirmed throughout seven years of clinical use. In fact, after withdrawal of digitalis, "...it may be the treatment of choice for digitalis-induced arrhythmias, provided hypokalemia is not present."[1] It has been widely used in selected supraventricular arrhythmias that have proved resistant to digitalis and in tachyarrhythmias precipitated by exercise, emotional stress, or undesirable sympathetic stimulation; and it is also effective in controlling supraventricular tachyarrhythmias related to the Wolff-Parkinson-White syndrome.[2]

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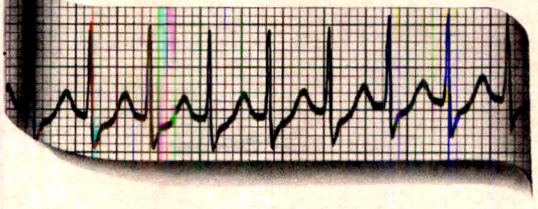
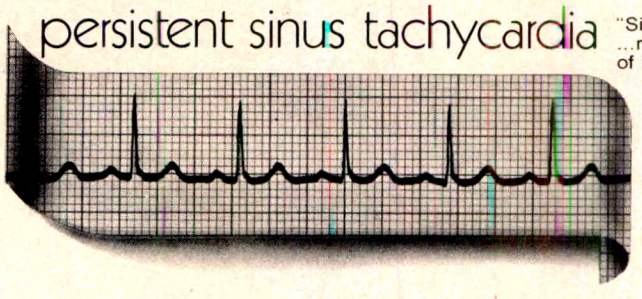
paroxysmal atrial tachycardia



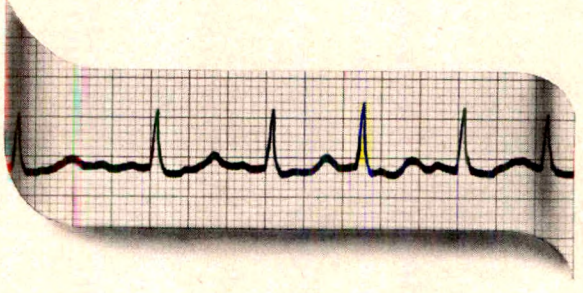
"In paroxysmal atrial tachycardia, the drug slows the ventricular rate, and also is valuable in restoring the heart to a regular sinus rhythm."[3] "Paroxysmal atrial tachycardia induced by exercise...has uniformly been prevented by propranolol," and results with INDERAL in the Wolff-Parkinson-White syndrome "...have been favorable in all but a few patients reported. This condition appears to be one of the more definite indications for propranolol."[4]

persistent sinus tachycardia



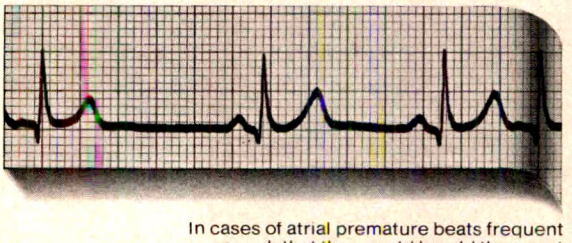
"Sinus tachycardia induced by stress ...may be inappropriate to the needs of the patient and, in fact, may be causing symptoms of itself. If the clinical situation does not suggest a needed compensatory sinus tachycardia and the heart rate is indeed inappropriate, treatment with propranolol has been successful."[4]

tachycardias and arrhythmias due to thyrotoxicosis



Although propranolol may accomplish only the reduction of the heart rate in hyperthyroidism, it has proved useful for this purpose. "Sinus tachycardia in hyperthyroidism which causes symptoms may be relieved by the administration of propranolol before definitive therapy....The author has observed that atrial fibrillation complicating hyperthyroidism was easily terminated using modest doses of propranolol."[4]

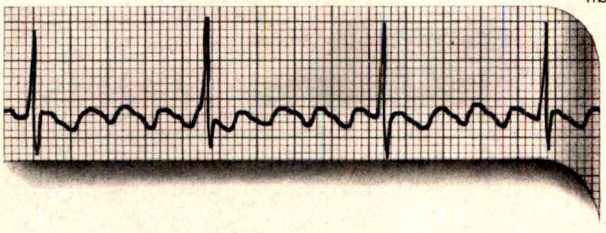
persistent atrial extrasystoles



In cases of atrial premature beats frequent enough that they could herald the onset of atrial fibrillation, it has been recommended that propranolol be used after other measures have failed to control the beats.[5]

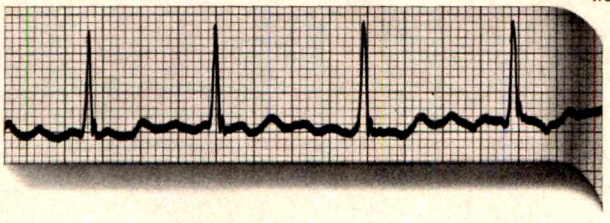
antiarrhythmia agents for supraventricular arrhythmias

atrial flutter



"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not controlled by digitalis, especially in the presence of mitral valve disease."[6]

atrial fibrillation

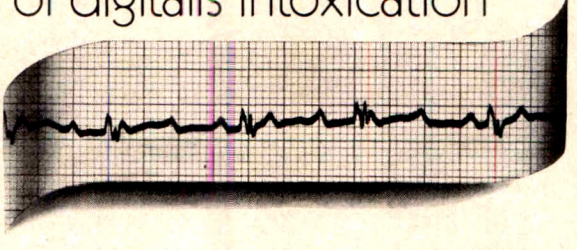


"One salutary effect of propranolol is slowing of the ventricular rate in atrial flutter and fibrillation."[4] In a review of the literature, it was noted that most patients with fibrillation not controlled by digitalis alone experienced slowing of the ventricular rate after administration of propranolol and a few reverted to sinus rhythm.[7]

---

and for tachyarrhythmias of digitalis intoxication

"Propranolol is very effective in treating arrhythmias caused by digitalis excess. Its use in this setting may be limited by the presence of significant congestive heart failure or heart block, both of which can be potentiated by propranolol. However, if given in small doses with careful monitoring, it is often of great value in the treatment of digitalis toxicity."[5]



References 1. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 2. Chung, E.K.: Postgrad. Med. *53*:107 (Apr.) 1973. 3. Harrison, D.C.: Clinical Guide to the Use of Beta-Adrenergic Blockade in Arrhythmias, Ayerst Laboratories, 1971, p. 10. 4. Reynolds, E.W.: Geriatrics *26*:150 (Feb.) 1971. 5. Helfant, R.H.: Med. Times *98*:118 (Jan.) 1970. 6. Sonnenblick, E.H.: Arrhythmias and Beta-Adrenergic Blockade, Ayerst Laboratories, 1971, p. 7. 7. Gibson, D., and Sowton, E.: Prog. Cardiovasc. Dis. *12*:16 (July) 1969.

Inderal®

Brand of propranolol hydrochloride

helps prevent or control catecholamine-induced cardiac arrhythmias

Ayerst.

AYERST LABORATORIES
New York. N.Y. 10017

BETA-BLOCKADE/**INDERAL®**
(propranolol hydrochloride)

(See last page of advertisement for prescribing information.)

BRIEF SUMMARY
(For full prescribing information, see package circular.)

Inderal®

Brand of
propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS:

Cardiac Arrhythmias

1.) Supraventricular arrhythmias
   a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)
   b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.
   c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
   May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)
   d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.
   e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
   Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.
   a) Ventricular tachycardias
   With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*
   b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
   If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.) Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia.
   Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis

INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg. daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED: BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride) TABLETS No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

7420

Schering

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.
Brand of DIAZOXIDE
INJECTION
20 ml ampule
contains 300 mg

"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ **Rapid reduction to normotensive levels**

Induces rapid reduction of blood pressure generally within 5 minutes... often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ **Prolonged activity**

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ **Protective action—helps avert target organ damage**

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ **Uncomplicated procedure**

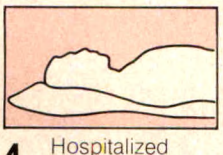
Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

☐ **Stable...convenient...no preparation**

HYPERSTAT I.V. Injection supplied in a 20 ml. ampule containing a stable solution of diazoxide 300 mg. ...ready to use.

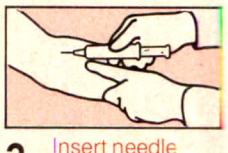
*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines



1. Hospitalized patient should be recumbent.

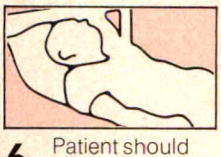
2. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml. ampule contains 300 mg. diazoxide).



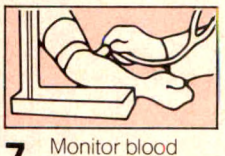
3. Insert needle only into a peripheral vein.

4. Inject entire dose I.V. in 30 seconds or less.

5. Remove needle carefully—avoid extravasation.

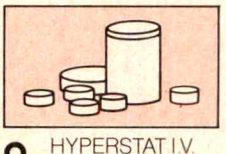


6. Patient should remain recumbent for at least half an hour after injection.



7. Monitor blood pressure closely until stabilized—usually 15-30 minutes.

8. If patient is to be ambulatory, blood pressure should be measured in standing position before surveillance is ended.



9. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective—generally within a few days.

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information on next page.

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.

Brand of DIAZOXIDE

INJECTION
20 ml. ampule
contains 300 mg

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

Description HYPERSTAT I.V. Injection is a rapidly acting antihypertensive agent. Each ampule (20 ml.) contains 300 mg. diazoxide, a nondiuretic benzothiadiazine derivative, in a clear, colorless, aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide. Diazoxide is 7-chloro-3-methyl-2H 1, 2, 4-benzothiadiazine 1, 1-dioxide.

Actions HYPERSTAT I.V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system.

Patients refractory to other antihypertensive agents usually remain responsive to diazoxide.

Diazoxide is extensively bound to serum protein (>90%). The plasma half-life is 28 ±8.3 hours; however, the duration of its antihypertensive effect is variable, generally lasting less than 12 hours. Although an antihypertensive response has been obtained with slow intravenous injection, in general, a greater antihypertensive effect is obtained with rapid intravenous administration.

Indications HYPERSTAT I.V. Injection is indicated for the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled.

HYPERSTAT (diazoxide) I.V. Injection is ineffective against hypertension due to pheochromocytoma.

Contraindications HYPERSTAT I.V. Injection should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt.

The drug should not be used in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

Warnings **Usage in Pregnancy:** The safety of HYPERSTAT I.V. Injection in pregnancy has not yet been established.

Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults.

Usage in Children: The safety of HYPERSTAT I.V. Injection in children has not yet been established.

Hypotension may occasionally result from the administration of HYPERSTAT I.V. If hypotension severe enough to require therapy occurs, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide.

Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. It should be noted that concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions).

Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent.

Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

Precautions HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available when HYPERSTAT I.V. Injection is used.

HYPERSTAT I.V. Injection should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively.

Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response.

As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental.

Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection.

Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

Adverse Reactions

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial and/or cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; unconsciousness, convulsions, paralysis, or confusion; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported.

Other adverse reactions: Nausea, vomiting, and/or abdominal discomfort; vasodilative phenomena, such as flushing, generalized or localized sensations of warmth, headache (sometimes throbbing), and sweating; orthostatic hypotension, lightheadedness, and weakness of short duration; supraventricular tachycardia and palpitation; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; nonanginal "tightness in the chest"; warmth or pain along the injected vein; cellulitis without sloughing and/or phlebitis at the site of extravasation; anorexia and alteration of taste; ileus; bradycardia; back pain; chest discomfort; dyspnea, choking sensation; apprehension or anxiety, malaise, and blurred vision occurred on single occasions; parotid swelling, salivation, lacrimation; ringing in the ears; diarrhea and constipation; increased nocturia; euphoria.

Drug Interactions Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

Overdosage Overdosage of HYPERSTAT I.V. Injection may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia.

Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

Animal Pharmacology and Toxicology In studies involving a number of species, including the rat, cat, dog, and monkey, diazoxide has been shown to exert significant antihypertensive actions through its direct effect on peripheral arterioles, which neither impairs cardiac function nor seriously diminishes perfusion of kidneys. In addition, in each species tested, including the rat, dog, and monkey, diazoxide elicits hyperglycemia, increased serum-free fatty acids and decreased plasma insulin levels by a mechanism thought to involve both suppression of insulin release and enhanced catecholamine action.

Although the data are not conclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period of embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term.

Dosage and Administration HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injection. It should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

The response to HYPERSTAT I.V. Injection varies from patient to patient. Generally, blood pressure decreases within five minutes, often within one to two minutes, to the lowest level achieved. The blood pressure increases relatively rapidly in the next ten to 30 minutes, and then more slowly over the following two to 12 hours, nearly reaching but rarely exceeding the pretreatment level. The response to successive injections is frequently better than that to the initial injection.

Treatment of hypertensive emergencies with HYPERSTAT I.V. Injection should be limited to a few days and a regimen of oral antihypertensive medications should be instituted as soon as possible.

With the patient recumbent, the contents of one 20 ml. ampule containing 300 mg. of HYPERSTAT I.V. Injection are administered intravenously in 30 seconds or less. Slow intravenous injection may fail to reduce the blood pressure or may produce an exceedingly short response.

Specific dosage is required in children or in unusually large or small patients. This dosage may be calculated on the basis of 5 mg./kg. body weight (0.3 ml./kg.) (See Warnings).

A second administration of HYPERSTAT (diazoxide) I.V. Injection may be required for a satisfactory reduction in blood pressure, if the first injection fails to give an adequate response within 30 minutes.

Repeated administration of HYPERSTAT I.V. Injection at intervals of four to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication becomes effective. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect will indicate any unusual response. A further decrease in blood pressure at 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain recumbent for half an hour after injection. In ambulatory patients, the blood pressure should be measured with the patient standing before surveillance is ended.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive failure.

How Supplied HYPERSTAT I.V. Injection is supplied in a 20 ml. ampule containing diazoxide 300 mg. in a clear, colorless aqueous solution; box of one ampule.

Protect from light and freezing.

Store away from heat.

AUGUST 1973

20 ml.
in 30 seconds or less
for direct action

SWW-4940

Schering

Schering Corporation
Kenilworth, N.J. 07033

Our new Cardiac Output Computer offers a lot more than meets the eye.

Digital display of cardiac output directly in liters per minute. That's the first feature physicians look for in our Model 9510 Cardiac Output Computer.

But in the ICU/CCU environment, where measurements of cardiac output via thermodilution are becoming increasingly important in the proper assessment of the critically ill, computer **versatility and accuracy** are major considerations.

In this respect, our new Model 9510 fills the need precisely. In the critically ill patient, clinical parameters can change rapidly. Accordingly, all instrument controls are front-panel mounted and can be easily adjusted in response to the subtle and changing conditions of the patient.

Both patient temperature **and** injectate temperature are dynamic variables. The ability to rapidly update and fine tune these variables to within 1/10°C., and the selection of various volumes of cold or room temperature injectate, facilitates precise and accurate clinical analysis.

Too, the Model 9510 was designed specifically for use with SWAN-GANZ® Flow-Directed Thermodilution Catheters. Their multilumen design allows assessment of right and left heart filling pressures, in addition to cardiac output.

Other major features include simplicity of operation, automatic integration of the dilution curve, provision for catheter circuitry checkout prior to insertion, and a portable, self-contained, battery-operated module, with total electrical isolation for patient safety.

For detailed specifications, clinical literature describing the thermodilution cardiac output technique, or a product demonstration, please write Edwards Laboratories, 17221 Red Hill Avenue, P.O. Box 11150, Santa Ana, California 92711, 714/557-8910, Cable: EDSLAB, Telex: 68:5567.

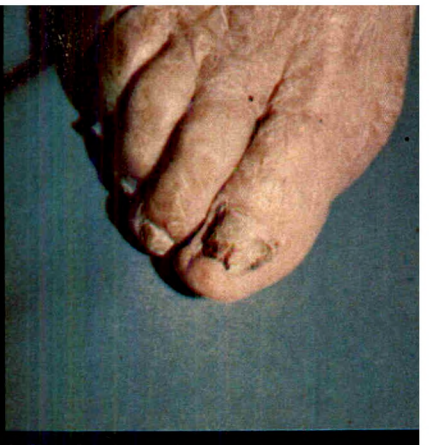
EDWARDS LABORATORIES®

Division of American Hospital Supply Corporation

USV VASO-QUIZ NO.1

What chronic vascular disorder do these photos and symptoms describe?

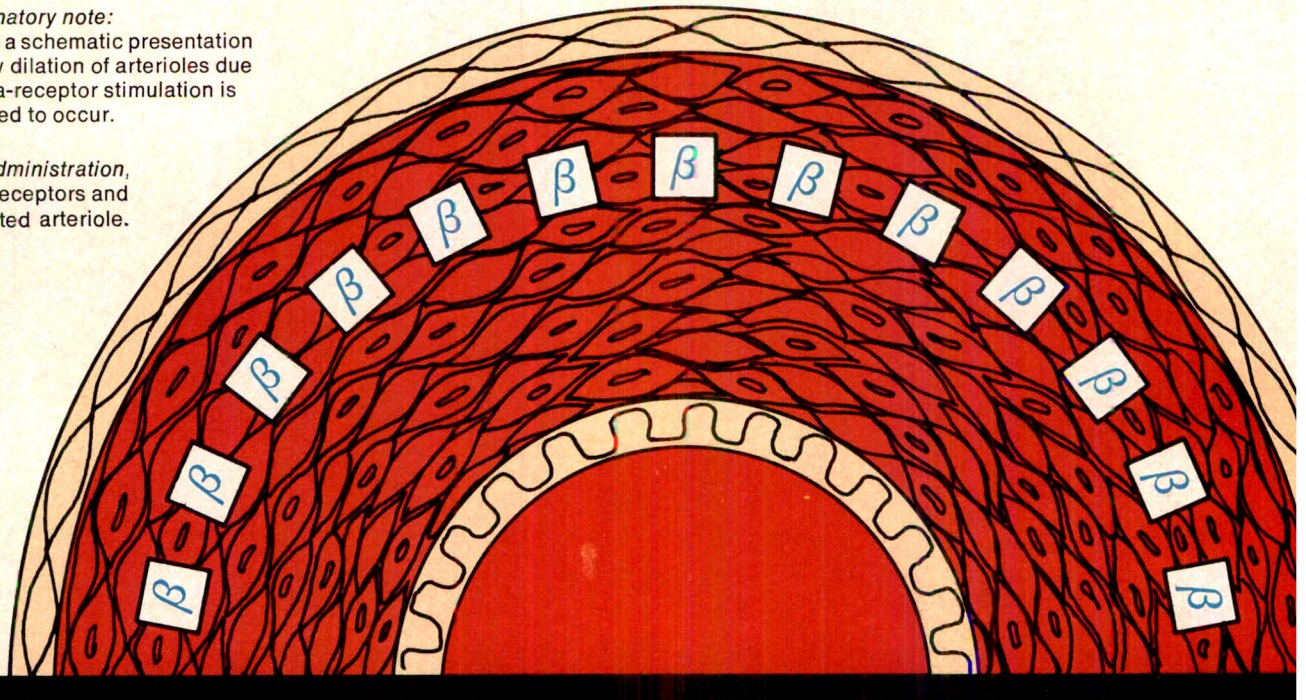
1. Characteristic symptoms due do malnourishment of the skin may include atrophic changes, scaly appearance and dryness. Hair is sparse on toes and dorsa of the feet.



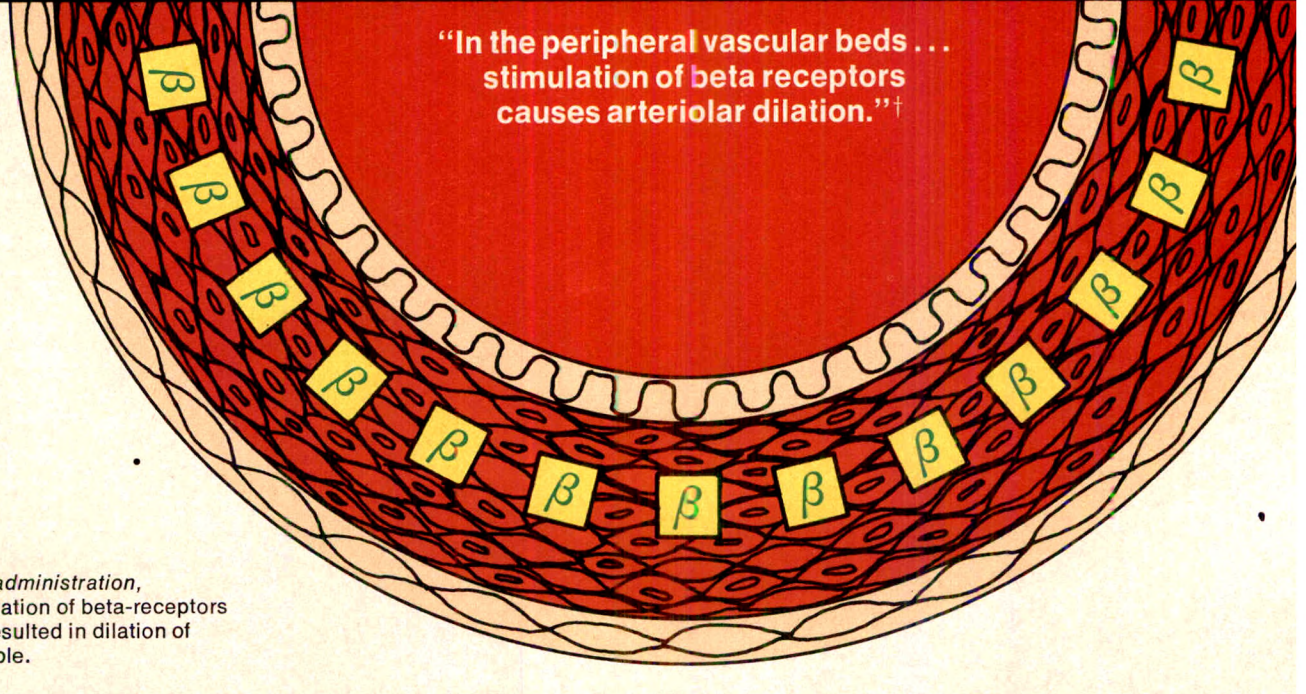
2. Impaired blood supply leads to characteristic nail changes: irregular growth, changes in shape and form and—common observed—slow growth.

Explanatory note:
This is a schematic presentation of how dilation of arterioles due to beta-receptor stimulation is believed to occur.

Pre-administration, beta-receptors and undilated arteriole.



"In the peripheral vascular beds . . . stimulation of beta receptors causes arteriolar dilation."†

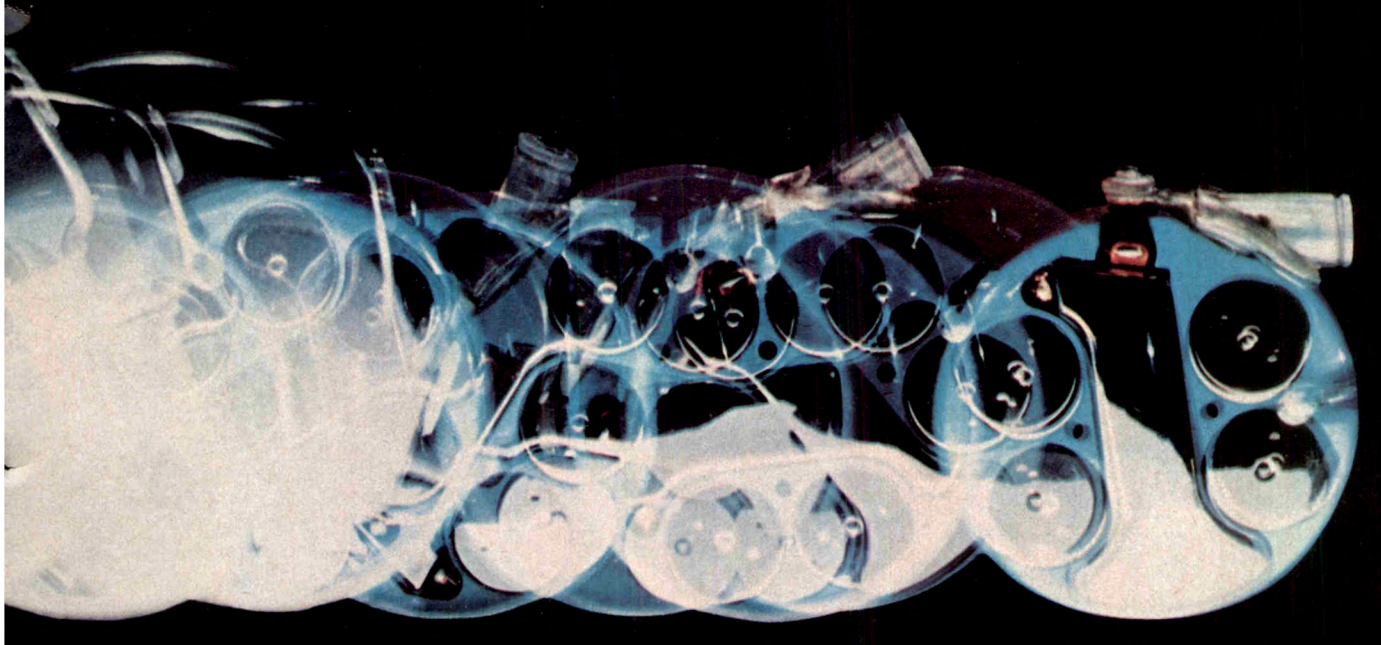


Post-administration, stimulation of beta-receptors has resulted in dilation of arteriole.

The New XYTRON™ Pulse Generator

It's a revolution, alright. Revolutionary in its smallness (illustration is actual size). And revolutionary in the fact that bipolar and unipolar models are now the same size.

The XYTRON™ pulse generator is evolutionary, too. It features the familiar quality, reliability and performance characteristics that today make Medtronic the pacemaker of choice throughout the world. With advantages like Energy Conservation and Energy Compensation. Plus the proven double-barrier power cell.



XYTRON™. A small revolution. The next logical step forward in pacemaking.

Medtronic maintains a worldwide network of offices and representatives to serve the medical profession. Check your local telephone directory.

Medtronic

THE PACEMAKER IN PACEMAKING

PROLONGED PROTECTION

SORBITRATE®
(ISOSORBIDE DINITRATE)
5 MG. AND 10 MG. ORAL q.i.d.

4-6 HOURS OF PROTECTION AGAINST ANGINA;* WORKS WITHIN 15-30 MINUTES.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Oral dosage forms of SORBITRATE are indicated for the relief of angina pectoris (pain of coronary artery disease). They are not intended to abort the acute anginal episode, but they are widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

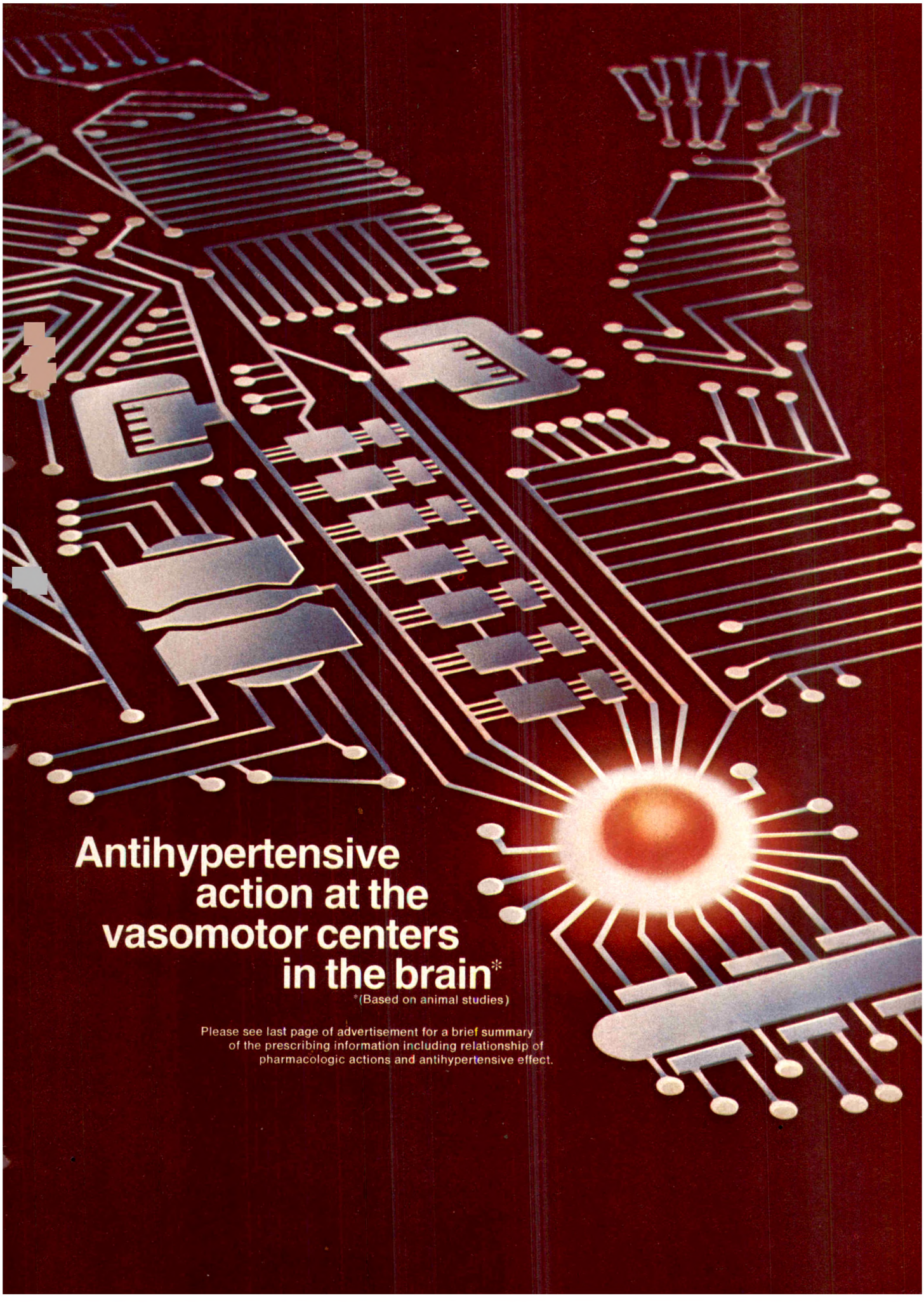
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS | Wilmington, DE 19897
Division of ICI United States Inc.



Antihypertensive action at the vasomotor centers in the brain*

*(Based on animal studies)

Please see last page of advertisement for a brief summary of the prescribing information including relationship of pharmacologic actions and antihypertensive effect.

Now... antihypertensive action at the vasomotor centers in the brain

new Catapres®

Tablets of 0.1 and 0.2 mg

(clonidine hydrochloride)

Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

Central action:

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardio-accelerator and vasoconstrictor centers in the medulla.

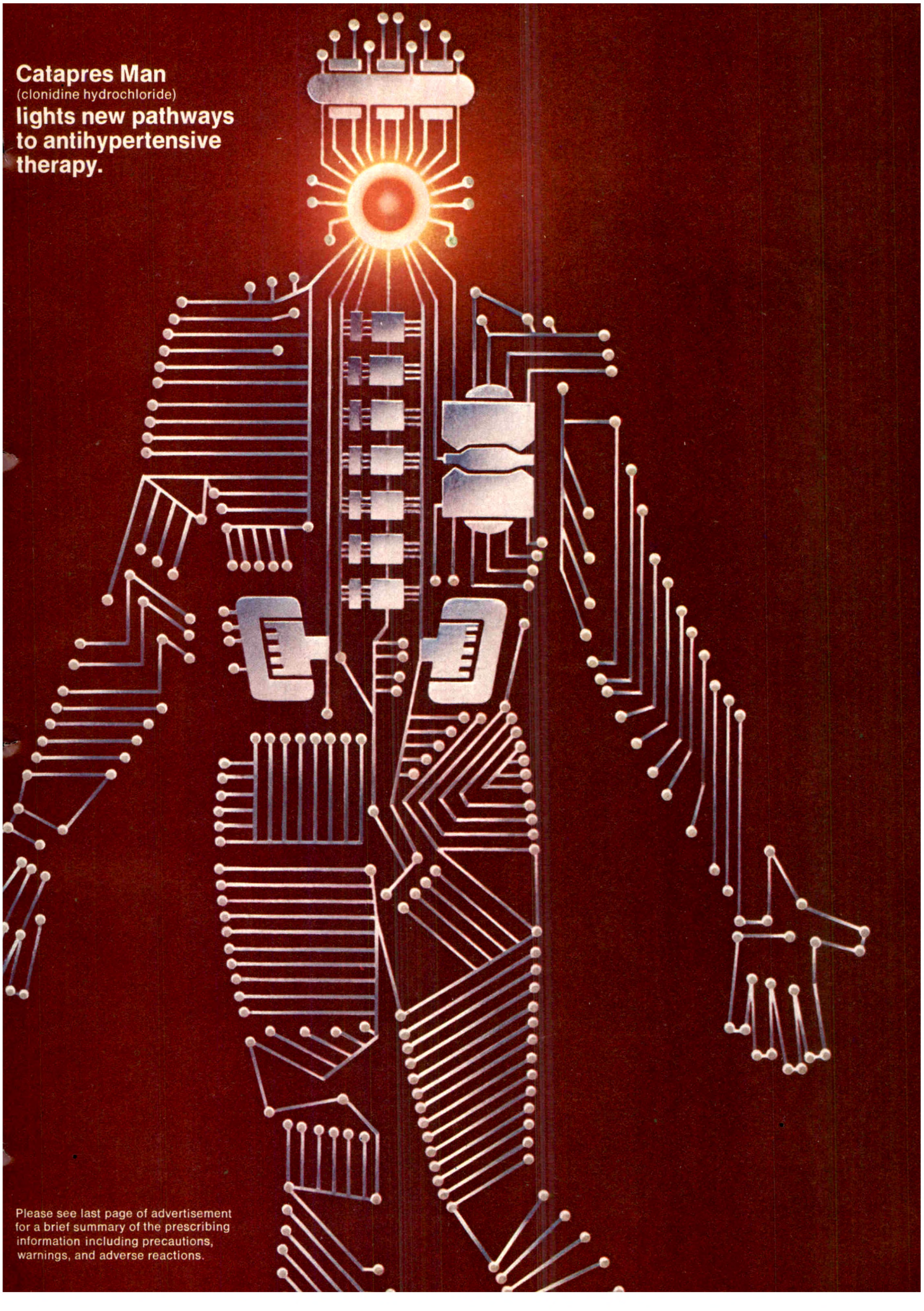
Not a "depleter"

Not a "blocker"

Not an "inhibitor"

Not a "false transmitter"

Catapres Man
(clonidine hydrochloride)
lights new pathways to antihypertensive therapy.



Please see last page of advertisement for a brief summary of the prescribing information including precautions, warnings, and adverse reactions.

new Catapres®
(clonidine hydrochloride)

Effective in hypertension, mild to severe

Catapres is distinguished by its broad clinical usefulness in the treatment of hypertension.

More than 600 major published papers*

The extensive experimental and clinical work with Catapres has been reported in hundreds of papers published in scientific journals in this country and abroad. Controlled studies[1-7] plus numerous other clinical evaluations have demonstrated that Catapres is an effective antihypertensive drug with these desirable properties:

does not alter normal hemodynamic responses to exercise

renal blood flow and glomerular filtration rate essentially unchanged

antihypertensive response enhanced by diuretics such as chlorthalidone

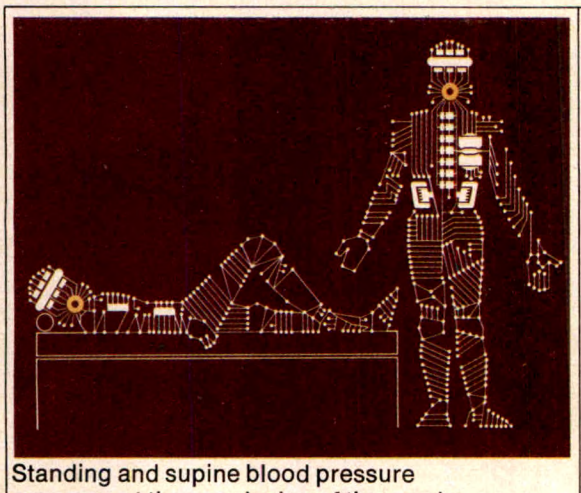
compatible with other antihypertensive agents

has been shown to reduce plasma renin activity and to decrease excretion of aldosterone and catecholamines
(See ACTIONS section of Brief Summary)

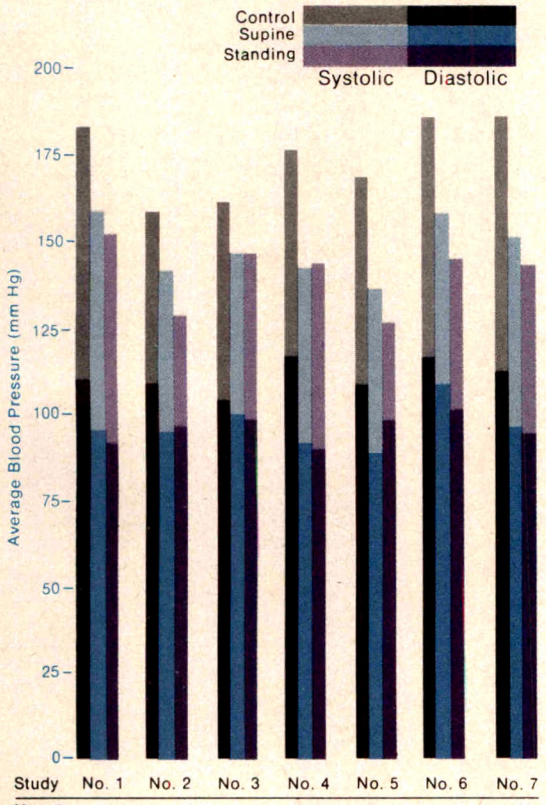
What to watch for—The principal side effects of Catapres are dry mouth, sedation, and drowsiness. Constipation, dizziness, headache, and fatigue also have been reported. Generally, these effects tend to diminish with continued therapy. As with other antihypertensive agents, tolerance may develop in some instances. For a more detailed discussion of side effects, warnings, and precautions, see the brief summary of prescribing information on the last page of this advertisement or consult the Catapres package insert.

*Complete Catapres bibliography available on request.

Mild and infrequent orthostatic effects



Standing and supine blood pressure response at the conclusion of therapy in 7 controlled studies[1-7]

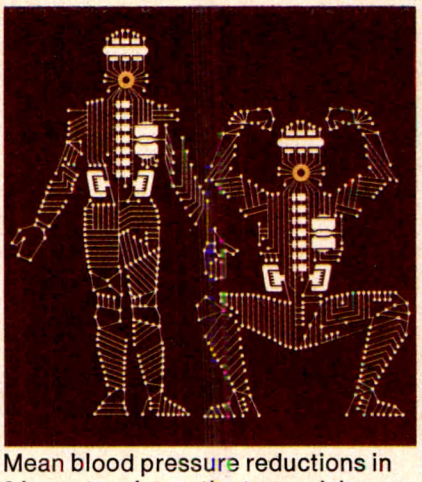


*Received Catapres alone.

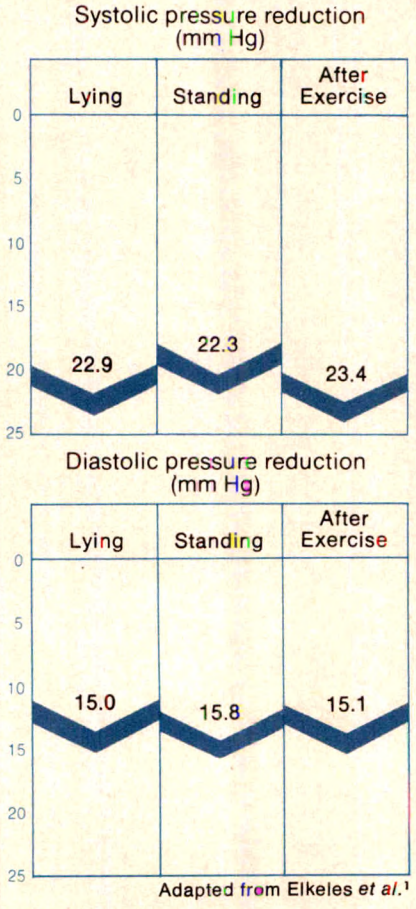
†Received Catapres + a diuretic.

Note: In study No.4, blood pressure was taken in the sitting rather than the supine position.

Normal hemodynamic responses to exercise not altered

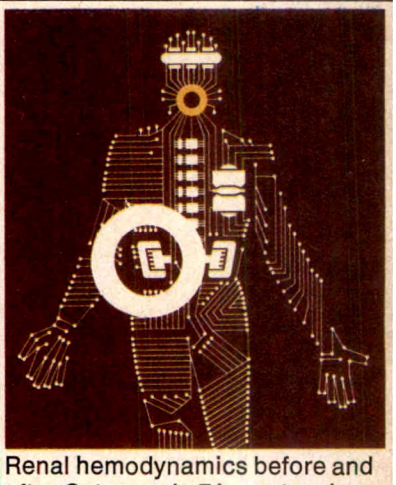


Mean blood pressure reductions in 9 hypertensive patients receiving Catapres (0.15 mg daily) for 4 weeks

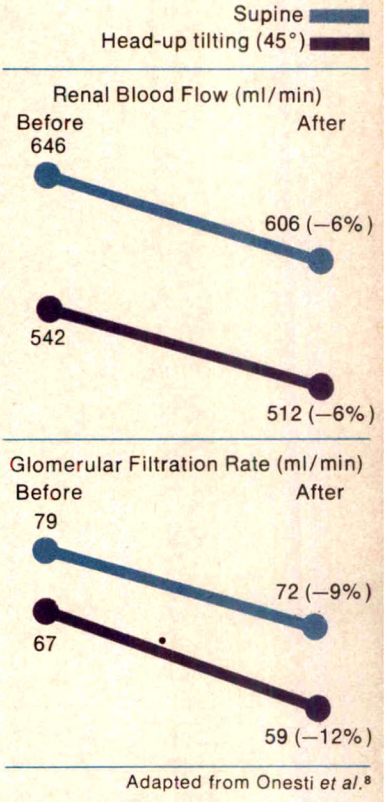


Adapted from Elkeles *et al.*[1]

Renal blood flow and glomerular filtration rate essentially unchanged

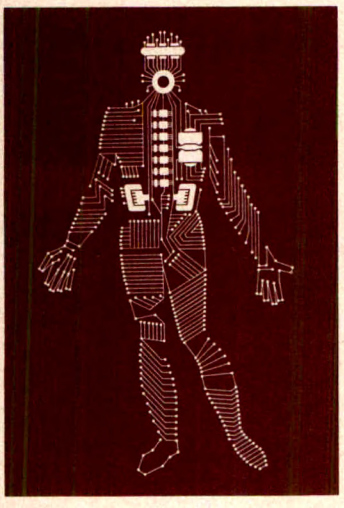


Renal hemodynamics before and after Catapres in 7 hypertensive patients. Mean blood pressure reductions were significant in both the supine position (from 155 to 128 mm Hg) and the standing position (from 151 to 101 mm Hg).



Adapted from Onesti *et al.*[8]

New from Boehringer Ingelheim



new Catapres®
(clonidine hydrochloride)

It's easy to start with Catapres. The usual starting dose of Catapres is one 0.1 mg tablet twice daily. Increments of 0.1 to 0.2 mg per day (up to the maximum daily dose of 2.4 mg) may be made until the desired blood pressure response is achieved.

How to stop Catapres. Reduce the dose gradually over two to four days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients on Catapres should be instructed not to discontinue therapy without consulting their physician. It has been demonstrated that a rapid rise in blood pressure, should it occur, can be reversed by resumption of Catapres or by administration of intravenous phentolamine.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Actions: The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic vasoconstrictor centers, thereby decreasing sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and ceath have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.
Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

References: 1. Elkeles, R. S., Goldby, F. S. and Oliver, D. O.: A Double Blind Study of Catapres, A New Hypotensive Agent, *in* Conolly, M. E. (ed.): Catapres in Hypertension, London, Butterworths, 1970, pp. 139-144. 2.Freis, E. D.: Data on file at Boehringer Ingelheim Ltd. 3. Hickler, R. B.: Data on file at Boehringer Ingelheim Ltd. 4. Mroczek, W. J., Leibel, B. A. and Finnerty, F. A., Jr.: Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic, Am. J. Cardiol. **29**:712, 1972. 5. Putzeys, M. R. and Hoobler, S. W.: Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients, Am. Heart J. **83**:464, 1972. 6. MacDonald, R. H. and Shapiro, A.: Data on file at Boehringer Ingelheim Ltd. 7. Kirkendall, W. M., Toubes, D. B. *et al.*: Hypertensive effects of clonidine and chlorthalidone, Am. Heart J. **82**:312, 1971. 8. Onesti, G. *et al.*: Pharmacodynamic effects of a new antihypertensive drug, Catapres (ST-155), Circulation **39**:219, 1969.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, New York 10523

The **new** Bentley Trantec Sterile Disposable Dome.

A major contribution to patient safety was made when the Bentley Trantec Pressure Transducer was introduced. Specifically, it incorporated the most effective electrical isolation available. ☐ Now, Bentley Trantec introduces the sterile disposable dome with an isolating diaphragm. An even higher degree of patient safety is achieved through the elimination of possible cross contamination. Domes come sterile-packed, to be quickly attached to the transducer, used, then discarded. Immediate and continuous use of the transducer is possible by simply changing the sterile dome — no further need for time consuming cleaning, wrapping, sterilizing and storing. ☐ The Sterile Disposable Dome. Another patient safety product from Bentley Trantec. Contact your Bentley representative or write for complete details.

BENTLEY TRANTEC, INC.
17502 Armstrong Avenue • Irvine, California 92705 • (714) 556-4464
A SUBSIDIARY OF BENTLEY LABORATORIES, INC.

The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Give enough, long enough—The recommended dosage: 50 mg t.i.d. at least one hour before meals for several weeks or longer.

Persantine® Tablets of 25 mg
dipyridamole

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

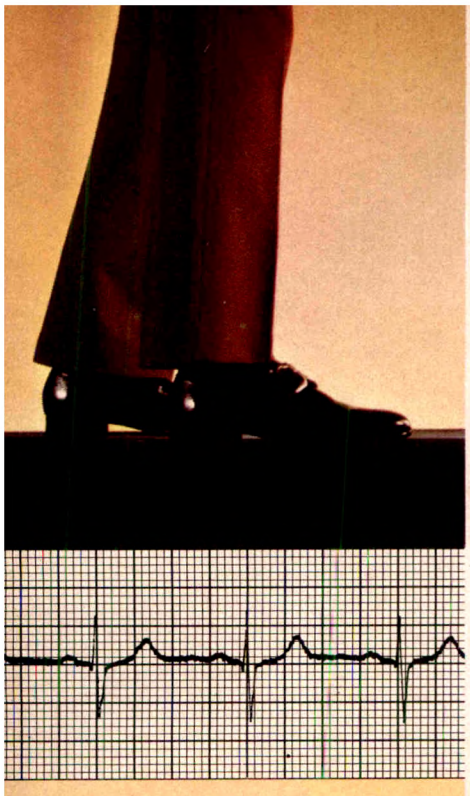
BOEHRINGER INGELHEIM

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, N.Y. 10523

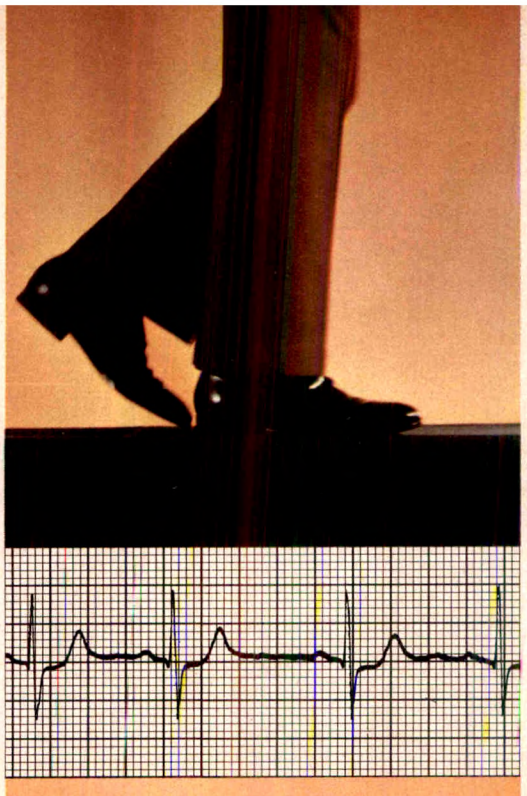
One of a series of paintings of the heart in the style of well-known artists.

The Heart... in the style of Henri Matisse (1869-1954)

Henri Matisse was one of the Fauve group and became a master of clear colors and *bonne peinture*. The closed surfaces, the choice of mostly pure colors and the simplicity of composition give his pictures an extraordinarily decorative effect.



Standing, at rest, V-5, HR-74. American's Stress Test Electrode supplies immediate base line stability. Testing with a narrow, drift free base line can begin as soon as the self-adhering, silver/silver chloride electrodes have been applied to the patient and connections made to your monitoring equipment.

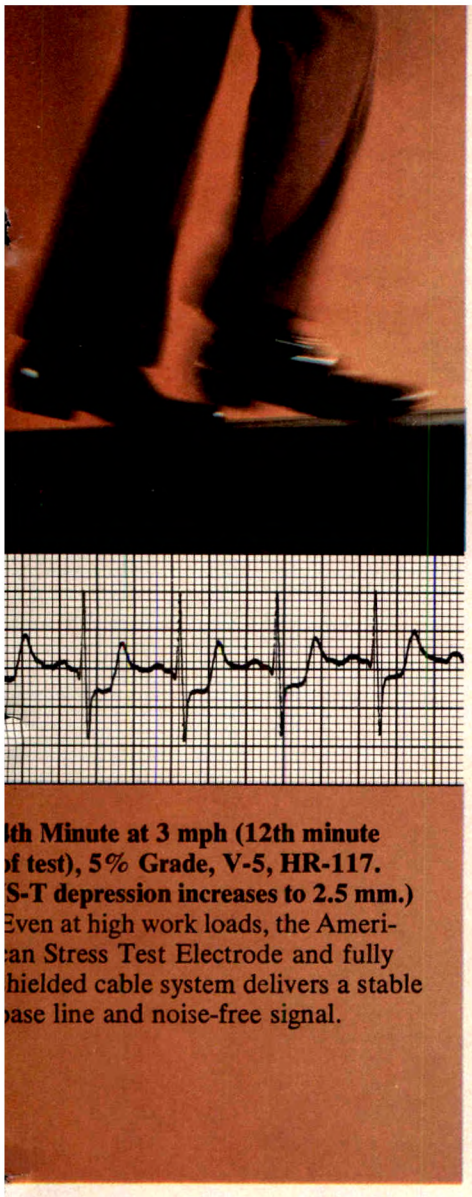


4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and impregnated foam pad which is slightly oversize to assure positive, continuous pressure at the electrode-skin surface. The results: immediate onset and virtual elimination of base line instability and motion artifact.

4th Minute at 3 mph (8th minute of test), 0% Grade, V-5, HR-83. (The patient's ECG indicates 1 mm of S-depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interferenc that might otherwise mask small amounts of S-T depression.

Finally.

An electrode/cable system specifically designed for stress testing.



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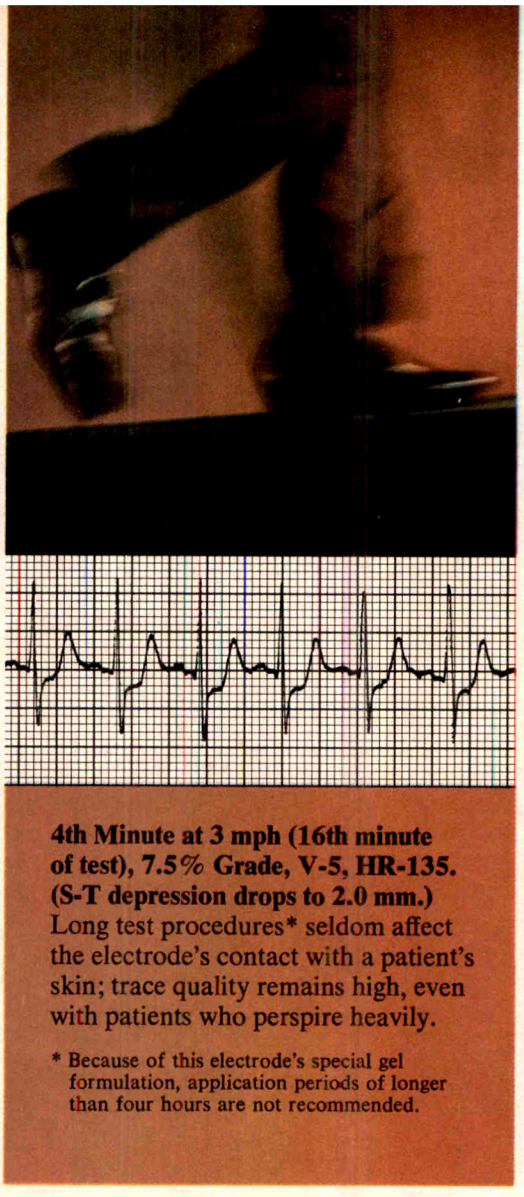

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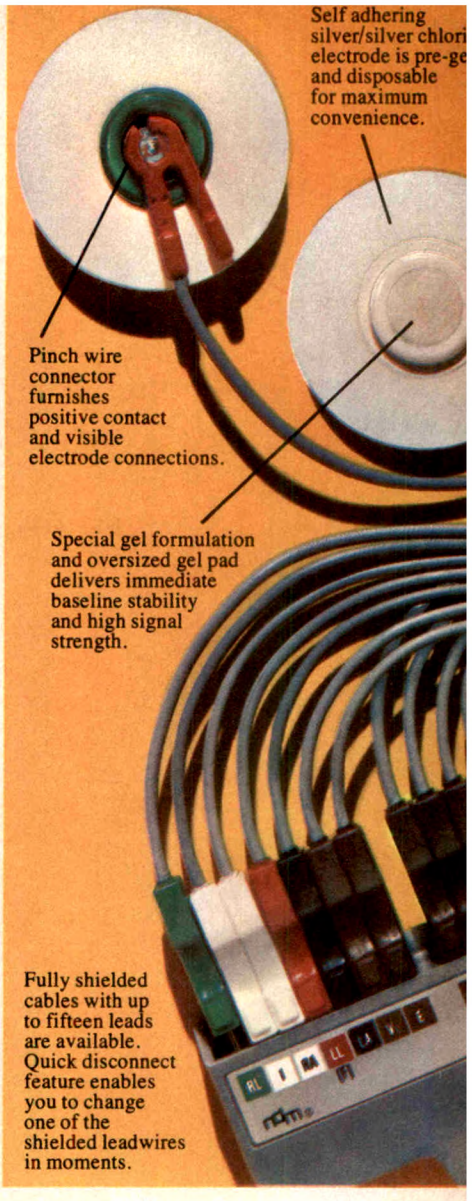

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See brief summary.

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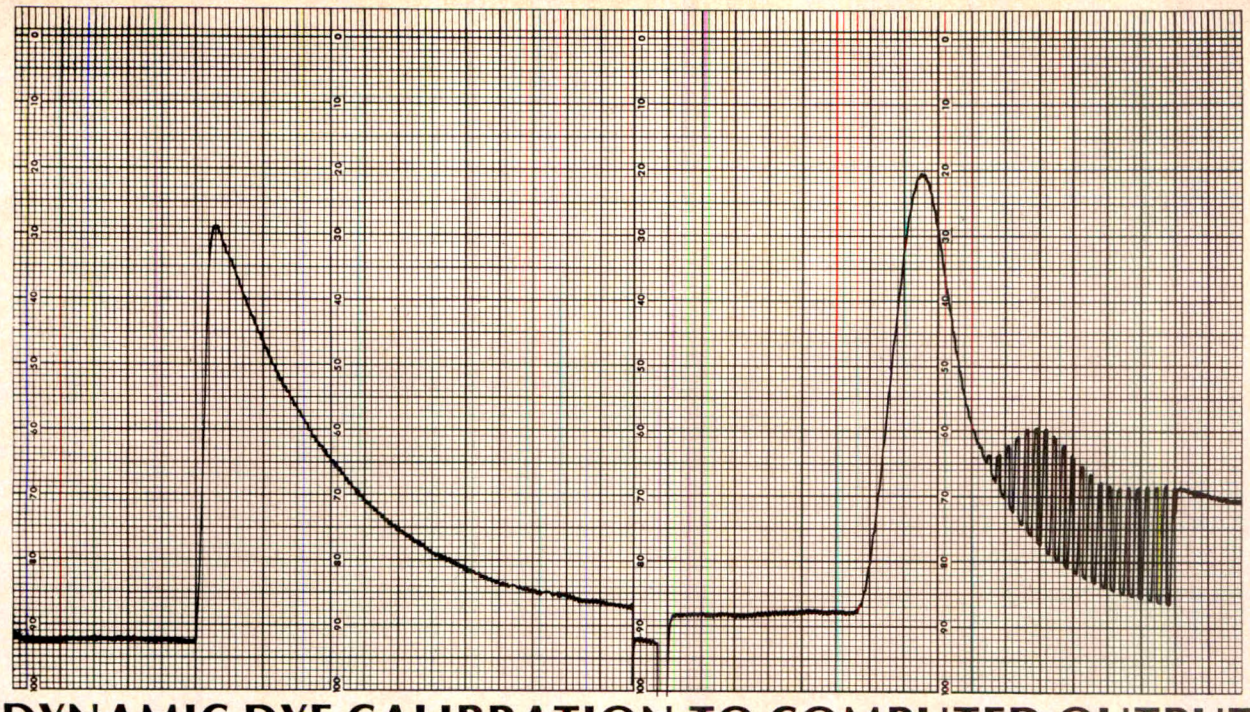

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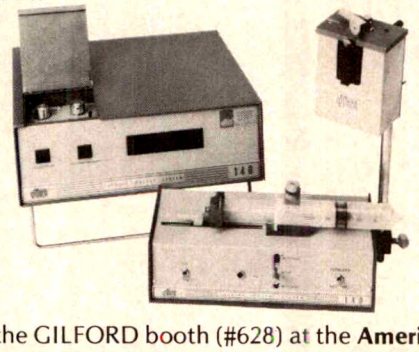

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Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

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*Manner, R. J.; Brechbill, D.O.; DeWitt, K.: Prevalence of Hypokalemia in Diuretic Therapy. Clin. Med. 79:15 (Nov.) 1972.

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tolerance to exercise improved for angina patients

INDICATIONS: For the prophylaxis and long-term management of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

PRECAUTIONS: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

SIDE EFFECTS: No serious side effects have been reported. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound.

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FEBRUARY 1975

The American Journal of CARDIOLOGY®

VOLUME 35

NUMBER 2

CLINICAL STUDIES

Atrioventricular and Intraventricular Conduction in Hyperkalemia

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JORGE C. RIOS, MD

Washington, D. C.

Twelve patients exhibited electrocardiographic evidence of fascicular block during hyperkalemia. Isolated left posterior hemiblock occurred in four, isolated left anterior hemiblock in two, right bundle branch block with left anterior hemiblock in two, right bundle branch block with left posterior hemiblock in one, left bundle branch block with abnormal left axis deviation in two and advanced atrioventricular block in one. In all seven patients with sinus rhythm the P–R interval shortened after correction of hyperkalemia. Electrophysiologic studies using His bundle recording and atrial pacing in one patient revealed intraatrial conduction delay and marked prolongation of conduction time in the His-Purkinje system. It is concluded that conduction defects in the specialized intraventricular conduction system are common in hyperkalemia and result in electrocardiographic patterns of fascicular block.

The electrocardiographic changes induced by hyperkalemia have received considerable attention because of the potentially lethal nature of this electrolytic abnormality. These changes may permit prompt recognition of hyperkalemia and may indicate its severity. In this communication we illustrate the spectrum of intraventricular conduction abnormalities associated with hyperkalemia and demonstrate that disturbances in the specialized intraventricular conduction system may play a significant role in these abnormalities.

Material and Methods

The electrocardiograms of 12 patients with hyperkalemia admitted to the wards of the D. C. General Hospital and the George Washington University Medical Center were studied. Tracings obtained during hyperkalemia and in close temporal relation to measurement of the highest serum potassium levels were analyzed and compared with tracings obtained after normalization of serum potassium. A His bundle electrogram was recorded in one patient who required temporary ventricular pacing because of repeated periods of sinus arrest. Atrial pacing was accomplished during hyperkalemia and 5 days later during normokalemia by placing the stimulating electrode against the high lateral wall of the right atrium in the region of the right atrial-superior vena caval junction. The acute nature of the illness in the other 11 patients precluded electrophysiologic investigations.

The patients ranged in age between 14 and 82 years; seven were male and five were female. The clinical, laboratory and electrocardiographic data are presented in Table I.

From the Division of Cardiology, Department of Medicine, The George Washington University Medical Center and The George Washington University Medical Division, D. C. General Hospital, Washington, D. C. Manuscript accepted July 17, 1974.

Address for reprints: Jorge C. Rios, MD, Department of Medicine, George Washington University Medical Center, 2150 Pennsylvania Ave., N.W., Washington, D. C. 20037.

Results

Rhythm: Seven patients had sinus rhythm with heart rates ranging from 46 to 150 beats/min. Four patients at the peak of their hyperkalemic state exhibited absence of P waves, suggesting either sinoventricular rhythm or junctional or idioventricular rhythm. Serum potassium values in these four patients ranged between 8.2 and 9.1 mEq/liter.

Atrioventricular conduction: First degree atrioventricular (A–V) block was present in three patients, with P–R intervals ranging from 0.22 to 0.24 second. One patient had transient advanced A–V

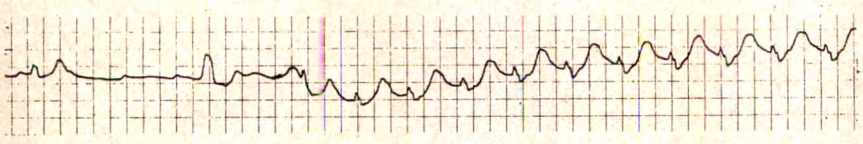

FIGURE 1. Case 10. Rhythm strip of lead II showing a period of advanced A–V block followed by apparent sinus rhythm (rate 96/min).

TABLE I

Clinical and Electrocardiographic Data

			Before Treatment						After Treatment			
				Electrocardiogram						Electrocardiogram		
Case no.	Age (yr) & Sex	Diagnosis	Serum K+ (mEq/liter)	Cardiac Rhythm & Rate (beats/min)	P-R (msec)	QRS (msec)	Intraventricular Conduction	Other	Serum K+ (mEq/liter)	P-R (msec)	Intraventricular Conduction	Outcome
1	19M	Overdose: methadone & secobarbital	8.0	SR, 90	220	100	LPHB	T	4.5	140	N	Lived
2	26M	Chronic renal failure, accelerated hypertension	5.7	SR, 92	230	80	LPHB	T	4.7	150	N	Lived
3	65M	Chronic renal failure	8.8	?SVR, 90	...	110	LAHB	T	4.8	170	N	Lived
4	28M	Alcoholic cirrhosis, bleeding esophageal varices, uremia	7.7	SR, 88	190	125	LAHB, RBBB	NSTC	4.2	130	N	Died
5	55F	COPD, CHF, progressive renal failure	8.4	?SVR, 70	...	120	LPHB, Inc. RBBB	T	4.6	200	Residual LAHB	Died
6	56M	Bronchogenic carcinoma with metastases, postoperative metabolic acidosis	9.2	SR, 130	180	85	LAHB	T, QS in V_1–V_3	5.1	140	N	Died
7	14M	Subarachnoid hemorrhage, acute renal failure	7.9	SR, 110	180	80	LPHB	T	5.5	160	N	Lived
8	50M	Hypertension, diabetes, ketoacidosis	8.1	SR, 150	160	80	LPHB	T	5.0	140	N	Lived
9	82F	Chronic renal failure, hypertension	9.1	?SVR, 75	...	180	LAHB, RBBB	T	5.1	170	N	Lived
10	33F	Acute and chronic renal failure	8.2	?SVR, 98	...	180	Transient advanced A-V block	...	4.7	...	...	Died
11	55F	Chronic renal failure	7.9	AF, 80–90	...	140	LBBB	...	5.1	...	N	Died
12	74M	Chronic CHF with azotemia	6.8	SB, 46	240	180	LAHB, LBBB	...	3.6	210	LAHB	Lived

AF = atrial fibrillation; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Inc. = incomplete; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LPHB = left posterior hemiblock; N = normal; NSTC = nonspecific T wave changes; RBBB = right bundle branch block; SB = sinus bradycardia; SR = sinus rhythm; SVR = sinoventicular rhythm; T = peaked T waves.

block (Fig. 1). In the patient whose His bundle electrogram was recorded during a serum potassium level of 6.8 mEq/liter (Case 12), the A–H interval was 142 msec and the H–V interval 100 msec, thus demonstrating a conduction delay predominantly in the His-Purkinje system (Fig. 2A). In the same patient a delay in intraatrial conduction was demonstrated by atrial pacing, which revealed an abnormally prolonged latency between the pacemaker spike and the onset of the *A* wave (Fig. 2B).

Intraventricular conduction: All 12 patients demonstrated some form of reversible abnormality in intraventricular conduction. Left posterior hemiblock, manifested by right axis deviation of more than +110° and clockwise inscription of the frontal QRS loop, was present in five patients (Fig. 3); in one it was accompanied by incomplete right bundle branch block. Left anterior hemiblock, manifested by a mean QRS axis of −45° or greater and a counterclockwise frontal loop, was also observed in five patients (Fig. 4); in two, it was associated with right bundle branch block (Fig. 5) and in one with left bundle branch block. One of the patients who manifested incomplete right bundle branch block and left

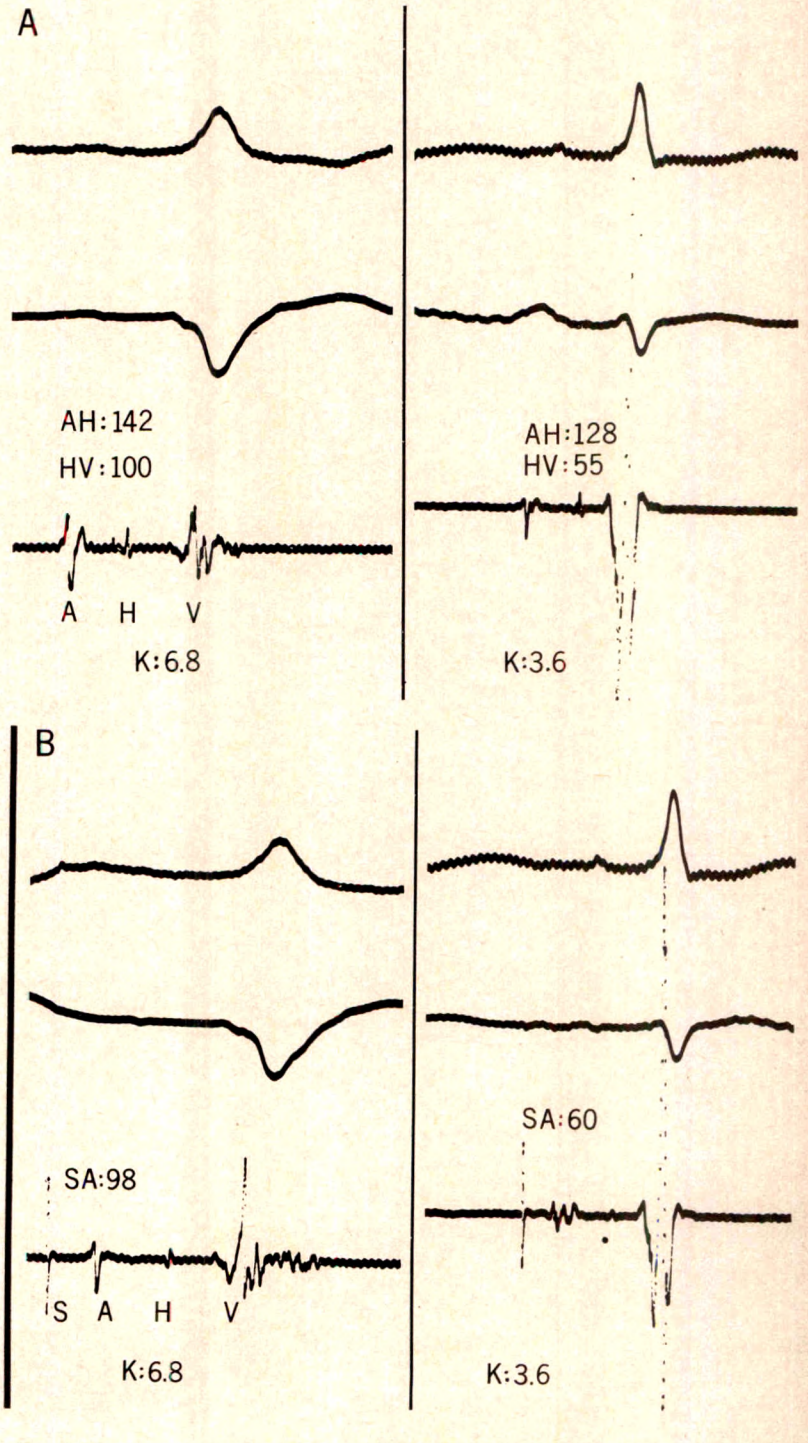

FIGURE 2. Case 12. **A,** simultaneous surface leads I and II and His bundle electrogram reveal marked prolongation of H–V interval during hyperkalemia. **B,** during atrial pacing. The time interval between electrical stimuli (S) and the resultant atrial activation (A) is markedly prolonged during hyperkalemia and shortens after normalization of serum potassium. A–H, H–V and S–A intervals in msec, potassium (K) in mEq/liter.

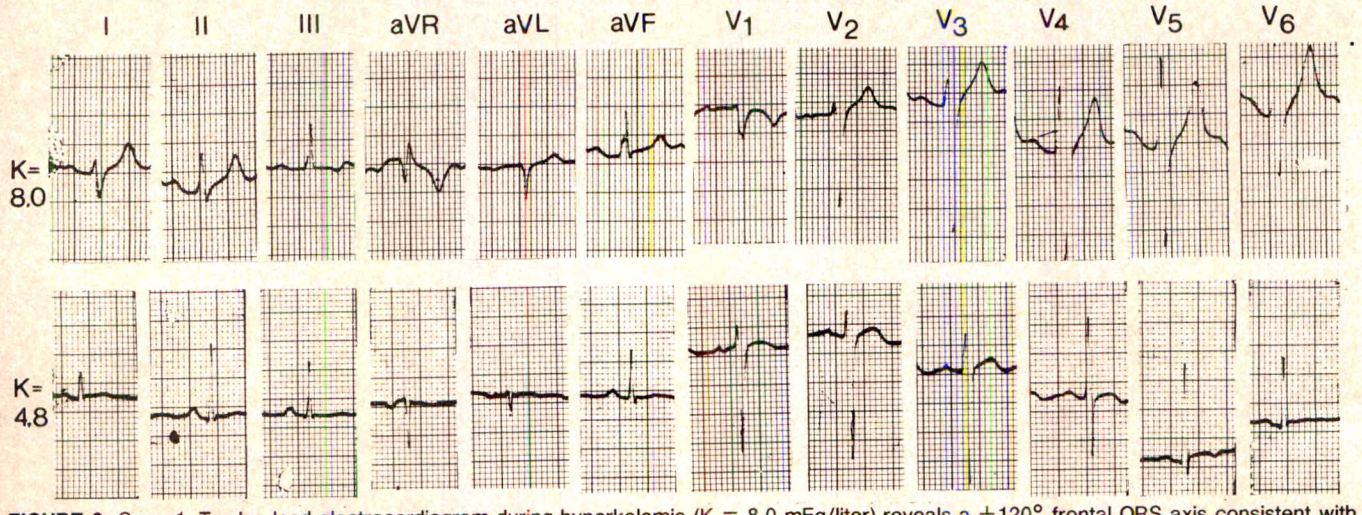

FIGURE 3. Case 1. Twelve lead electrocardiogram during hyperkalemia (K = 8.0 mEq/liter) reveals a +120° frontal QRS axis consistent with left posterior hemiblock. First degree atrioventricular block is also present (P–R interval 220 msec). With normalization of serum potassium, both atrioventricular and intraventricular conduction defects were abolished.

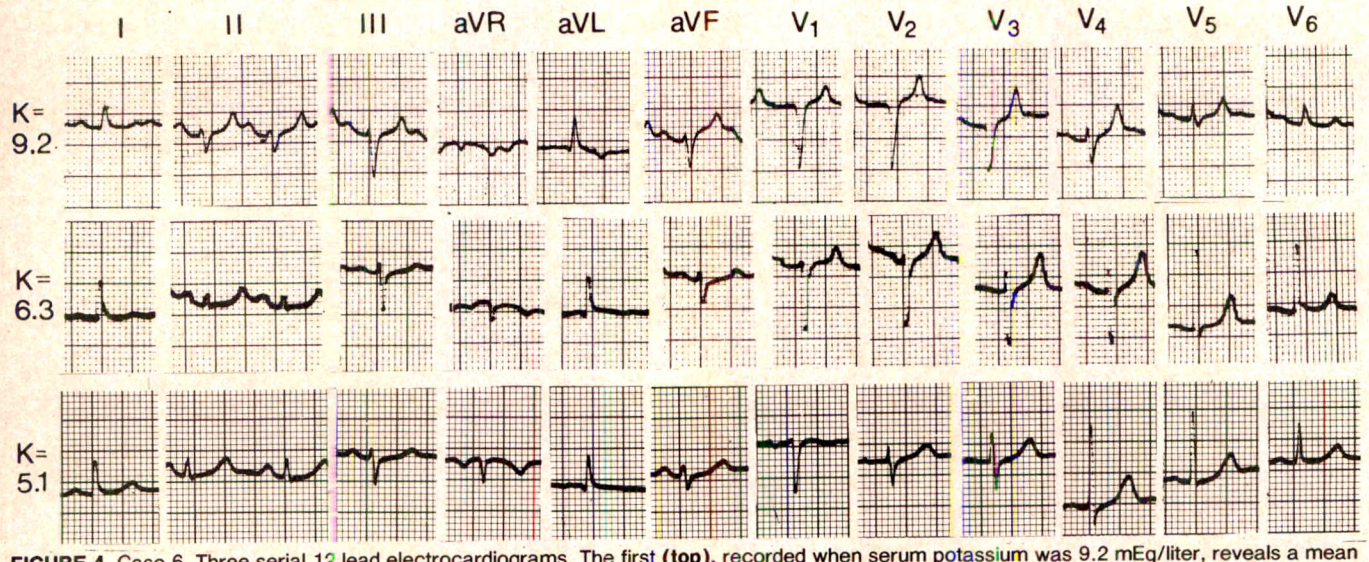

FIGURE 4. Case 6. Three serial 12 lead electrocardiograms. The first **(top)**, recorded when serum potassium was 9.2 mEq/liter, reveals a mean frontal QRS axis of −45° with counterclockwise inscription of the initial forces consistent with left anterior hemiblock. The second tracing **(middle)**, recorded when serum potassium was 6.3 mEq/liter, reveals almost complete normalization of the QRS axis and shortening of the P–R interval. The third tracing **(bottom)** is entirely normal.

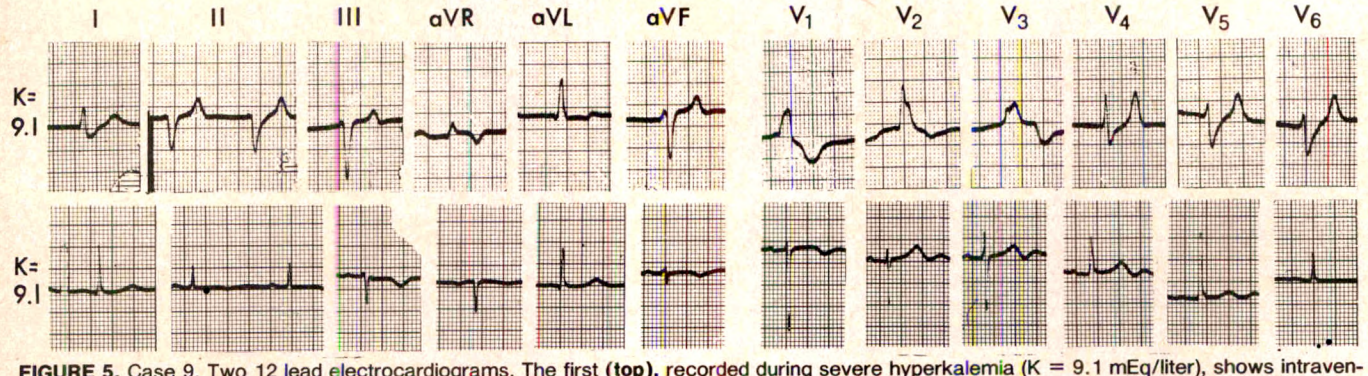

FIGURE 5. Case 9. Two 12 lead electrocardiograms. The first **(top)**, recorded during severe hyperkalemia (K = 9.1 mEq/liter), shows intraventricular conduction defects manifested by right bundle branch block and left anterior hemiblock. After correction of hyperkalemia **(bottom)** all conduction abnormalities were reversed.

posterior hemiblock during hyperkalemia had a preexisting left anterior hemiblock that persisted after correction of hyperkalemia. One patient had isolated left bundle branch block.

Discussion

The electrocardiographic manifestations of hyperkalemia are ascribed to shortening in the duration of the transmembrane action potential, lowering of the resting membrane potential and increased velocity of phase 3.[1] The changes in the duration of action potential and velocity of phase 3 are considered to be the cause of the characteristic narrowing and peaking of the T wave and shortening of the Q–T interval observed when serum potassium exceeds 5.5 mEq/liter.[2]

Further elevations of serum potassium decrease the rate of rise (dV/dt) of phase 0 and result in slower ventricular depolarization,[3] thus interfering with impulse conduction within the myocardial muscle fibers of both the atria and ventricles. Sensitivity to hyperkalemia is maximal in the atrium, less in the ventricle and is least in the specialized conduction system.[4,5] Accordingly, impaired conductivity of the atrial myocardium may result in sinoventricular rhythm.[6,7] In cases of severe hyperkalemia, abnormalities in ventricular depolarization are due to impairment of impulse transmission along the specialized ventricular conduction system as well as in the myocardial fibers. The appearance in hyperkalemic patients of conduction defects that mimic fascicular blocks has been described,[8–11] but we are aware of only one previous His bundle electrocardiogram obtained in a patient during hyperkalemia[10]; in that study a delay proximal to the His bundle was observed. In our patient intraatrial and His bundle electrograms indicated prolonged conduction times in the atria since the interval from the pacing spike to the low atrial sensing electrode (S–A interval) was much longer than normal[12–14] and the prolongation was reversible after correction of hyperkalemia. Prolonged A–V nodal and especially prolonged His-Purkinje conduction times reversible after correction of hyperkalemia were also observed. In experimental hyperkalemia in the dog, multiple areas of A–V block could be identified by His bundle recordings.[15]

In an earlier study by one of us,[16] it was noted that P–R intervals were often relatively prolonged during the hyperkalemic state and were consistently shortened with correction of hyperkalemia. P wave changes manifested by decreased P amplitude and increased P duration were also reversed as hyperkalemia was corrected by hemodialysis. It was postulated that the changes reflected conduction impairment in the atrial myocardium due to hyperkalemia.

The present study illustrates the multifaceted nature of the intraventricular conduction defects in hyperkalemia and demonstrates by means of His bundle electrocardiography performed in one patient that prolongation of the P–R interval may be caused by conduction delay at any level within the conduction system.

Acknowledgment

We express our appreciation to Mrs. Marlyn Baran for her patient typing of the manuscript.

Addendum

Since submission of this manuscript, we have learned of a study in which two patients with hyperkalemia manifested block above the bundle of His (Cohen H, Rosen K, Pick A: Disorders of impulse conduction and impulse formation caused by hyperkalemia in man. Am Heart J, in press).

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Blood Platelet Response to Plasma from Patients with Ischemic Heart Disease

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Blood platelets change shape (from small round spheres to larger spread forms) as they participate in thrombosis. Using an electron microscopic technique, we surveyed 14 patients with both acute and chronic ischemic heart disease; each had increased spread platelet forms (69 ± 22.2 [standard deviation] percent) when compared with 14 asymptomatic control subjects ($P < 0.001$). When platelets from these 14 control subjects were exposed to plasma from the patients with ischemic heart disease, spread forms increased from 13.4 ± 9.1 to 44.5 ± 15.5 percent ($P < 0.001$). There was no significant increase in spread platelets in these control subjects when their blood was mixed with plasma from another control group. Similar studies were performed in seriously ill noncardiac patients; 9 of 13 had increased spread platelet forms when compared with control subjects, but plasma from only 5 of these 9 subjects caused increased spread forms when mixed with platelets from normal subjects ($P < 0.05$).

Thus a factor existed in the plasma of these patients with ischemic heart disease that caused normal platelets to become spread. Similarly the plasma of some patients with serious noncardiac disease had a comparable effect on normal platelets. Although the identity of this factor is unknown, it is probably unrelated to hormonal or therapeutic influences occurring either during acute infarction or during the stress of serious illness because (1) the effect of the plasma from patients with acute ischemic heart disease was identical to that of patients with chronic ischemic heart disease, and (2) the effect was not present in all patients with serious noncardiac disease.

Blood platelets change shape as they aggregate. This fact has been confirmed by several investigators utilizing transmission[1,2] and scanning[3] electron microscopes. Such changes in configuration, from round dense disks that develop extrusions or pseudopods to large less dense spread forms, may be assessed accurately using an electron microscopic technique[1]

To explore further this platelet response, we used this method to study the effect of platelet-poor plasma removed from patients with ischemic heart disease on platelets harvested from asymptomatic control subjects. Similar studies were performed using platelet-poor plasma from 13 patients with serious or life-threatening illnesses of noncardiac origin.

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Materials and Methods

Patient Selection

Acute myocardial infarction: Seven patients admitted consecutively to the Cardiac Care Unit of the University of Michigan Hospital were studied. Acute myocardial infarction had been confirmed by appropriate electrocardiographic and serum enzyme changes. Platelet studies were performed within 48 hours of admission. The age range was 40 to 71 years (mean 56 years). There were five men and two women.

Chronic ischemic heart disease: Seven patients with either healed myocardial infarction (occurring more than 3 months previously) or chronic angina pectoris were studied. The age range was 43 to 76 years (mean 54 years). There were six men and one woman.

Control Subjects

Volunteers from hospital personnel without symptoms of cardiovascular illness were selected during the study of each patient. These control subjects were excluded if they had ingested aspirin-containing drugs or antihistaminic agents within the preceding 7 days. In addition, women using oral contraceptive agents were exempted. These subjects were not age-matched with patients and base-line electrocardiograms were not obtained from them.

Whole Platelet Morphologic Studies

Peripheral blood samples were obtained by venipuncture and collected into sterile disposable syringes. The first 2 ml was withdrawn and the syringe detached. A second syringe, containing 1 ml of 3.8 percent sterile sodium citrate, was immediately attached to the tubing and 9 ml of whole blood was withdrawn. The anticoagulant agent was mixed gently and briefly with the whole blood sample. Finally, the mixture was transferred to a 6 oz. polyethylene wide-mouthed bottle. A nonfrosted microscope slide, coated previously with a thin film of Formvar® (1 percent polyvinyl Formvar in ethylene dichloride), was introduced into the bottle, which was placed horizontally in a 37° C oven for exactly 8 minutes. The slide was then immersed in cold 1 percent buffered osmium fixative for 15 minutes at room temperature to stabilize the cellular elements that had adhered to the Formvar film. After fixation, the slide was rinsed in several changes of distilled water and then dried. Next, the edges of the slide were scraped with a no. 22 Bard-Parker blade to free the Formvar film. The platelet population adhering to the surface of the film was surveyed with a phase microscope, and stainless, 200 mesh specimen grids were placed over representative areas. Specimen grids were placed so that their concave surfaces contacted the Formvar film. A thin film of condensed moisture was formed over the film by vigorous exhaling at close range. Immediately, a piece of plastic tape was stretched over the preparation and rubbed firmly. When the tape was removed, the Formvar film became detached from the surface of the slide and covered the concave surface of the specimen grids. Adherent platelets on the surface of the Formvar film were in contact with the surface of the grids, which were removed by rimming their circumference with a blade and then lifting with a pair of tweezers. Preparations were then viewed with an electron microscope.

Platelet Types

Blood platelets that adhered to the surface of a Formvar film during the 8 minutes of incubation exhibited structural alterations including the extrusion of pseudopodia, hyalomeric fusion and hyalomeric spreading. Three distinct types of platelets were observed. The round type was compact, had a smooth contour and was uniformly electron-dense. Dendritic types were characterized by a compact electron-dense central area from which were extruded either a few short blunt pseudopodia or several long pseudopodia (Fig. 1). The spread type was increased in size with only a few of the pseudopodial tips obvious. The central area was less dense or was entirely electron-translucent (Fig. 2).

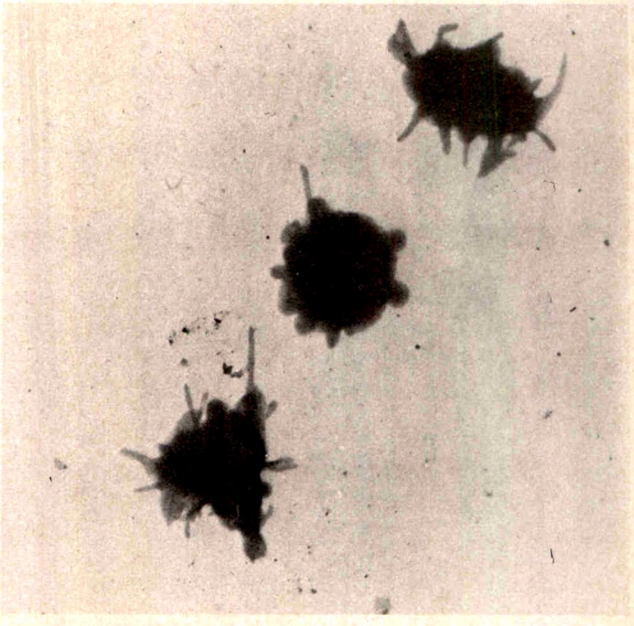


FIGURE 1. Electron micrograph of three dendritic platelets, indicating only minimal platelet activation. (×5,100, reduced by 35 percent.)

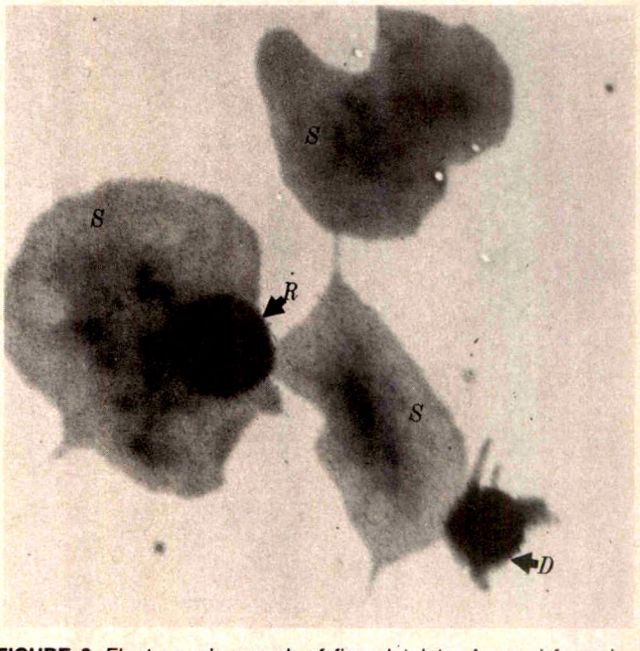


FIGURE 2. Electron micrograph of five platelets. A round form, labeled R, is superimposed over one spread platelet(S), and a dendritic form, labeled D, is contiguous with a spread platelet form. Spread forms indicate increased platelet activation. (×5,100, reduced by 39 percent.)

TABLE I

Clinical Data and Percent Spread Platelets from 13 Seriously Ill Patients Without Underlying Cardiac Disease

Case no.	Age (yr) & Sex	Condition	Spread Platelets (%)
1	42F	Chronic renal insufficiency	48
2	60F	Septic shock	87
3	61M	Amyloidosis	35
4	37M	Ulcerative colitis	39
5	62M	Abdominal abscess	74
6	19M	Suicide attempt (coma)	48
7	57M	Tracheotomy	63
8	39M	Pneumonitis	38
9	51M	Possible brain tumor	57
Mean ± SD			(54.2 ± 17.7)
10	23F	Respiratory insufficiency	24
11	57M	Chronic renal insufficiency	19
12	68M	Severe metabolic acidosis	22
13	22M	Hepatic pre-coma	9
Mean ± SD			18.5 ± 5.8

SD = standard deviation.

One hundred successive platelet types were categorized. A platelet differential count was performed twice on each blood sample, and the mean of two observations was obtained. To avoid the possibility of bias, each grid containing platelets for examination was coded so that the person surveying the grid was unaware of the source of the sample. Such labeling was not performed by those making the electron microscopic observations.

Plasma Transfer Experiments

After selection of the patient, blood was removed to determine ABO blood group and Rh type. Two asymptomatic subjects with the same blood type were then selected. An ABO and Rh cross-match was made between each of these three subjects to avoid the potential of platelet activation due to the formation of antigen-antibody complexes.

The following procedures were then performed:

I. In each of the three subjects to be studied (patient, control subject 1, control subject 2):
   A. 3 ml of blood was removed for platelet count.
   B. 9 ml of blood was prepared for whole mount platelet study as described.

II. From the patient and control subject 2:
   A. 9 ml of blood was drawn into a syringe to provide 3 ml of platelet-poor plasma, which was subsequently maintained at room temperature.

III. The following studies were then performed:
   A. From the patient, 6 ml of blood was drawn into a syringe preloaded with 1 ml of sodium citrate and with 3 ml of platelet-poor plasma from control subject 2. The sample was then prepared for electron microscopic examination of platelets.
   B. From control subject 1:
      1. 6 ml of blood was drawn into a syringe preloaded with 1 ml of sodium citrate and 3 ml of platelet-poor plasma derived from the patient. This sample was subsequently prepared for electron microscopic examination of platelets.
      2. 6 ml of blood was drawn into a syringe preloaded with 1 ml of sodium citrate and 3 ml of platelet-poor plasma harvested from control subject B. This sample was subsequently prepared for examination in the electron microscope.

Volunteers designated control subject 1 were separated at random into control groups A and C. Those designated control subject 2 were separated into control groups B and D (see Results).

Results

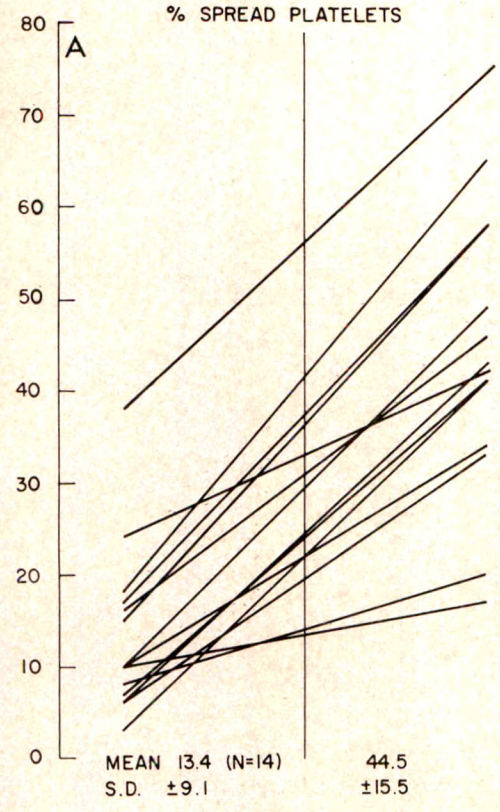
The seven patients with acute myocardial infarction had a preponderance of spread platelet forms (71.2 ± 19.3 [standard deviation] percent), as did the seven patients with chronic ischemic heart disease (68.6 ± 16.4 percent) (four with chronic angina pectoris, three with healed infarction and one with both). No significant correlations were observed between the magnitude of platelet activation (numbers of spread forms) and the clinical and laboratory status (electrocardiograms and serum enzyme, cholesterol and triglyceride determinations).

Plasma Transfer Experiments

Patients with ischemic heart disease: A significant increase in the number of spread platelet forms was observed when blood from asymptomatic subjects (control group A) was exposed to the platelet-poor plasma of patients with ischemic heart disease (from 13.4 ± 9.1 to 44.5 ± 15.5 percent spread forms, $P < 0.001$) (Fig. 3A). When blood samples from these asymptomatic subjects were mixed with platelet-poor plasma of another group of asymptomatic subjects (control group B), there was no significant change in the number of spread platelet forms (Fig. 3B). However, when plasma from asymptomatic control subjects was mixed with platelets from patients with ischemic heart disease, no significant decrease in the number of spread forms was observed (from 60.9 ± 22.2 percent to 49.3 ± 26.6 percent).

Studies in seriously ill patients without heart disease: Table I lists the age, sex, condition and platelet differential counts for each of the 13 subjects with serious illness of noncardiac origin. Patients 1 to 9 demonstrated a significant increase in number of spread forms (54.2 ± 17.7 percent), but patients 10 to 13 had a normal number of spread forms (18.5 ± 5.8 percent).

The plasma from the patients without cardiac disease was mixed with the blood of asymptomatic control subjects (group C) and a variability in platelet response was observed. When platelet-poor plasma from Patients 1 to 9 was mixed with the platelets from control subjects (control group C) there was a generalized increase in percent of spread forms (from 19.8 ± 9.6 percent to 35.3 ± 19.1 percent). This



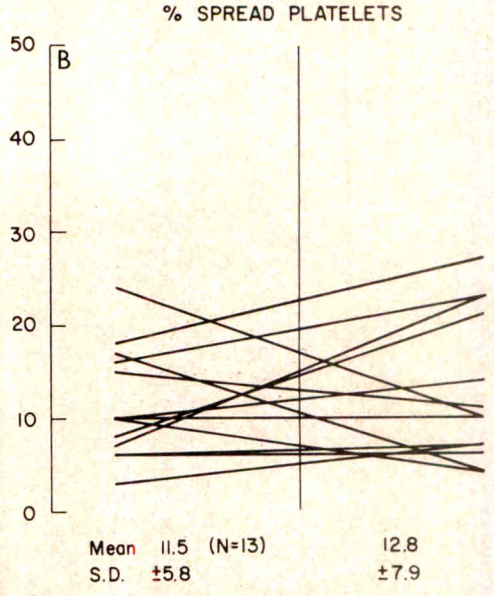
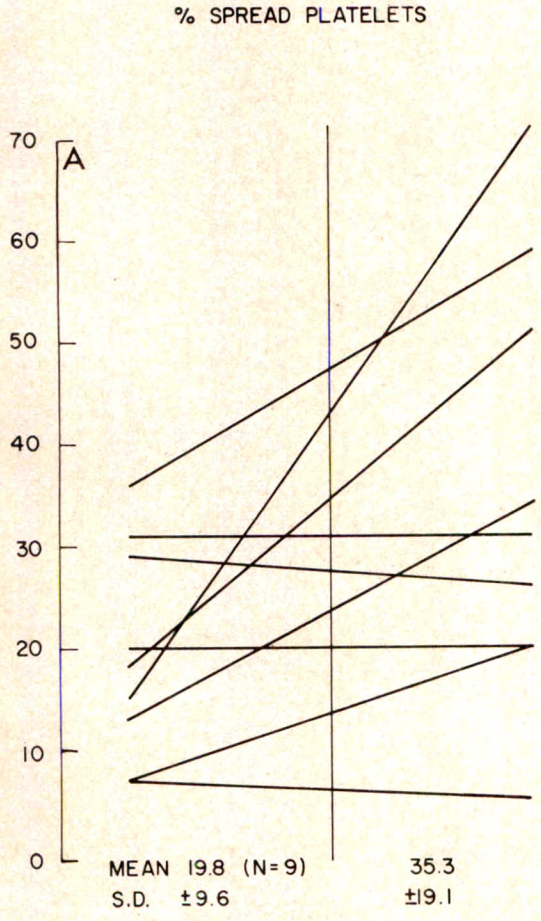


FIGURE 3. Change in percent of spread platelets from control subjects (group A). **A,** before and after mixing with plasma from patients with ischemic heart disease. Control values are to left, and results after mixing are to the right of the vertical axis. There is a significant increase in spread platelets after exposure to patient plasma ($P < 0.001$). **B,** before and after mixing with plasma from other control subjects (group B). S.D. = standard deviation. These data demonstrate no significant change in percent of spread platelets.



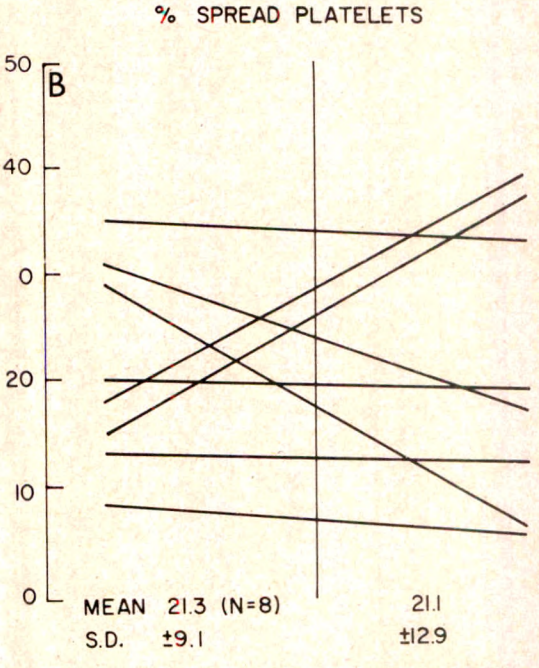


FIGURE 4. Change in percent of spread platelets. **A,** from control subjects (group C1) before and after mixing with plasma from nine seriously ill patients without underlying cardiac illness. Each of these nine patients had an increased percent of spread platelets (mean 54.2 ± 17.7 percent). The change in total number of spread forms approaches statistical significance ($P < 0.05$), but there is greater variability for each individual experiment (in four subjects there was no change or a slight decrease in percent spread forms). **B,** from the same control subjects before and after mixing with plasma from other control subjects (group D1). The change is not significant.

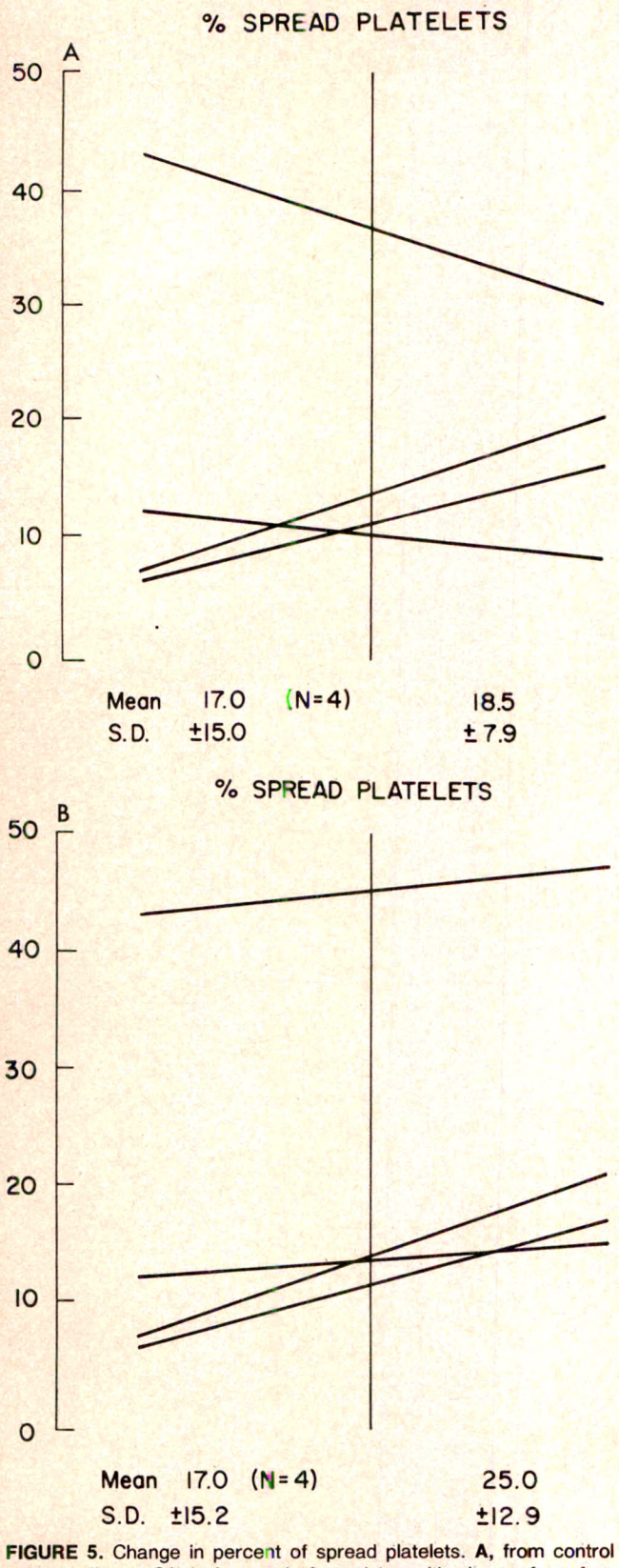


FIGURE 5. Change in percent of spread platelets. **A,** from control subjects (group C2) before and after mixing with plasma from four seriously ill patients without cardiac disease and a normal number of spread platelets (18.5 ± 5.8 percent). **B,** from the same control subjects before and after mixing with plasma from other control subjects (group D2). There is no significant change after mixing in either study.

change appeared to be statistically significant at the 0.05 level, using the Wilcoxon Signed Rank test[4] (Fig. 4A). A control experiment in which platelets from control group C were exposed to plasma from another control group resulted in no significant change in percent of spread platelets (Fig. 4B). Patients 10 to 13 had no indication of platelet activation and there was no detectable difference in spread platelet forms from control group blood when exposed to plasma from these patients (Fig. 5, A and B).

Discussion

Platelet Function and Vascular Disease

Clumping and fusion of blood platelets are the earliest visible manifestations of arterial thrombosis. Accordingly, investigations into the function and structure of platelets have been pursued actively for at least two practical reasons: first, because inhibition of platelet aggregation may be a possible means of preventing arterial thrombosis and, second, because it is possible that the continual laying down of microthrombi on the intimal surface of arteries represents an important and fundamental cause of atherosclerosis.[5]

The evidence that platelet function is altered in patients with atherosclerotic vascular disorders is contradictory. We have observed increased spread platelet formation in all of a group of patients with acute myocardial infarction and in approximately 50 percent of these patients for up to 18 months after infarction.[6,7] Similarly, the majority of a group of patients with chronic angina pectoris had increased spread forms.[8] Recently, Salky and Dugdale[9] observed persistent platelet hyperresponsiveness to collagen in 5 of 47 patients with ischemic heart disease 10 to 16 months after infarction. Other investigators have demonstrated increased platelet adhesiveness or platelet aggregation, or both, in ischemic heart disease by using various methods of measuring platelet function; these include rotating aliquots of platelet-rich plasma at 33 revolutions/min at an angle of 45° in the refrigerator,[10] measuring the length and weight of a thrombus within a closed rotating circular plastic loop,[11] observing the stressed template bleeding time and the amount of platelet retention in a column of glass beads,[12] and tabulating the number of platelet aggregates in the coronary circulation of patients who died suddenly.[13] Other investigators found no detectable change in platelet adhesiveness or platelet function by studying adenosine diphosphate-induced platelet adhesiveness to glass beads,[14,15] measuring platelet survival by the chromium-51 method,[16] or observing platelet aggregometry using the commercially available aggregometer.[16]

Another approach to the problem of defining the relation of platelet function and vascular disease was described by Bolton et al.,[17] who identified in the plasma from patients with arterial disease a "transferable factor" that caused an abnormal sensitivity to

adenosine diphosphate by normal platelets.[17] These investigators concluded that this factor had two components—(1), a low density lipoprotein, the active moiety of which was lecithin, and (2) an enzyme that converted the lecithin to lysolecithin. They speculated that the lysolecithin induced an abnormal platelet sensitivity to adenosine diphosphate as measured by a maximal increase in platelet electrophoretic mobility. A subsequent report has described an "aggregating material" in the plasma of "healthy individuals."[18]

Platelet Morphologic Studies

Our observations depend upon two facts: Platelets change shape immediately after blood is removed from the circulation, and these changes are a morphologic expression of platelet surface activation. Clearly, the dimensions of the interaction that occurs between the platelets and the polyvinyl plastic Formvar are unknown; nevertheless, even if this interface provides an artificial stimulus for platelet morphologic change, such provocation is present for blood from asymptomatic subjects as well as from patients.

A plasma factor causing platelet activation: Is it valid to conclude that the plasma of patients with ischemic heart disease contains a separate and potentially identifiable factor that causes platelets to become activated? Although the control experiments disclosed no signs of increased platelet activity when plasma from asymptomatic subjects was mixed with normal platelets, there was a discrepancy between the mean age and age range of the control subjects and those patients who were studied. It is thus conceivable that the plasma factor is a normal accompaniment of age; this possibility has not been excluded by appropriate experiments in which platelets from control subjects were exposed to plasma of another group of control subjects, each age-matched for the patients under study. However, this seems highly unlikely to us since in a survey of 18 asymptomatic subjects over age 40 years, platelet configuration was not significantly different from that in 67 asymptomatic subjects under age 40 years (unpublished data).

The presence of a plasma factor causing platelet activation in some but not all of 13 patients with serious noncardiac disease is unexplained. The plasma of each of 14 patients with ischemic heart disease demonstrated this effect, yet it was observed in only 5 of those 9 patients without heart disease who had an increased number of spread platelets. This finding indicates that a preponderance of spread platelet forms is not always accompanied by a transferable platelet-activating plasma factor. Thus, one might speculate that spread platelet formation may be the morphologic reflection of a final common pathway of functional platelet response to a number of different stimuli.

Effect of hormonal and stress situations during acute infarction: A further inference from these data would be that platelet activation and the transferable plasma factor are probably not the direct result of hormonal or therapeutic influences during the stress of infarction. No significant difference in the effect of plasma from patients with chronic ischemic heart disease (measured at least 3 months after myocardial infarction in four patients) and from patients with acute infarction was demonstrated. Since higher plasma levels of catecholamines occur during the first days of acute myocardial infarction,[19] we suggest that these substances are probably not responsible for the changes observed. There were no data to suggest that the seven patients with chronic ischemic heart disease were under any particular stress that would have caused increased plasma catecholamines.

Similarly, it is well known that plasma catecholamines increase in various stress situations, including hemorrhage[20] and shock.[21] It is probable that each of the 13 seriously ill patients without cardiac disease in this series was sufficiently stressed to have high levels of plasma catecholamines, yet increased platelet activity, and particularly the plasma factor, was found in only some of these patients.

Clearly, further studies are required to identify and isolate this plasma factor, to determine its relation to the lysolecithin described by Bolton et al.[17] and to examine whether platelets are uniformly responsive to its influence.

Acknowledgment

Dr. Jairus D. Flora of the University of Michigan School of Public Health provided valuable statistical advice. We also acknowledge the technical assistance of Patricia Saine, Linda Nork, Carol Cartwright and Virginia Carr.

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Coronary Arteriographic Findings in 1,000 Women Under Age 50

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In a consecutive series of 1,000 women under age 50 examined by coronary cinearteriography principally for evaluation of chest pain, 236 had at least 50 percent narrowing of one or more coronary arteries. The youngest, and the only patient who died, was 26 years old. The anterior descending coronary artery was the vessel most frequently involved; the right coronary artery was most often totally occluded. The amount of arterial involvement seemed to be related to the duration of symptoms.

Only 10 percent of women with serum cholesterol levels under 200 mg/100 ml had significant coronary artery disease, whereas 44 percent of those with levels over 275 mg/100 ml had significant disease.

Electrocardiographic evidence of myocardial infarction was uncommon in women with single vessel disease, but left ventriculograms disclosed that additional patients had areas of decreased contractility. Eleven of 46 women with electrocardiographically diagnosed myocardial infarction had no significant coronary artery disease. The cause of the electrocardiographic finding remained obscure in some.

Although there was an excellent correlation of clinical diagnoses with arteriographic findings in women thought not to have angina pectoris, only half of those thought to have angina pectoris had significant coronary artery disease. This finding may be a major reason for recommending coronary arteriography for the evaluation of angina-like pain in women under age 50.

The characteristics of a group of 1,000 unselected patients studied by selective coronary cinearteriography have been reported,[1–3] and a subsequent report[4] considered a series of men under age 40. This communication is concerned with 1,000 women less than 50 years old, an age chosen to correspond approximately to that of menopause. We were again interested in the distribution of significant lesions, correlation with cholesterol levels, electrocardiographic and ventriculographic evidence of infarction or impaired contractility related to lesions of different arteries, the phenomenon of infarction without significant arterial narrowing, extent of disease related to duration of symptoms, and the correlation of clinical diagnoses with the presence of significant lesions.

Methods

The records of 1,000 women under the age of 50 years consecutively examined by selective coronary cinearteriography[5] from 1961 through 1968 were evaluated; 976 women were studied to determine the cause of chest pain but many of these had additional indications such as elevated serum cholesterol levels, arrhythmias or conduction disturbances, congestive heart failure, dyspnea or syncope. Only 24 did not have chest pain. Patients with congenital or valvular heart disease or muscular subaortic stenosis were not included; those with hypertension and those with primary myocardial disease were included.

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TABLE I

Distribution of Significant Coronary Arterial Lesions

Location	no.	%
LCA only	10	4.2
+ LAD	1	0.4
+ LCx	0	...
+ RCA	4	1.7
+ LAD + LCx	1	0.4
+ LAD + RCA	2	0.8
+ LCx + RCA	2	0.8
+ LAD + LCx + RCA	5	2.1
LAD only	60	25.4
+ LCx	17	7.2
+ RCA	30	12.7
+ LCx + RCA	57	24.2
LCx only	10	4.2
+ RCA	16	6.8
RCA only	21	8.9
Total	236	(23.6% of 1,000)

LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

TABLE II

Number of Affected Coronary Arteries per Patient

	Women < Age 50		Men < Age 40[4]	Unselected Series[2]
	no.	%	(%)	(%)
Affected arteries per patient (no.)				
1	101	43	36	34
2	68	29	31	37
3	62	26	31	27
4	5	2	2	3
Total patients (no.)	236	...	357	588
Total arteries (no.)	443	...	706	1170
Affected arteries per patient (average no.)	1.9	...	2.0	2.0

The records were first examined without reference to cardiac catheterization findings, and clinical diagnoses were assigned as outlined previously.[4] Other characteristics including age, cholesterol levels, electrocardiograms at the time of catheterization, and the duration of symptoms were also determined. Electrocardiographic criteria for myocardial infarction were restricted to QRS changes of transmural myocardial infarction.

The catheterization findings were then tabulated. A lesion was classified significant[1] if the arterial lumen was narrowed by at least 50 percent. The presence of decreased contractility of regions of the left ventricle was determined by left ventriculography, a procedure that became routine in 1963.

Results

Incidence of Coronary Artery Disease

Two hundred thirty-six (23.6 percent) of the 1,000 women under age 50 had significant narrowing of at least one coronary artery. This small percentage contrasts with the figures of 59 percent in the group unselected by age or sex[2] and 49 percent in the series of young men.[4] The difference probably relates to the greater difficulty in evaluating the characteristics of the chest pain in this group of women, as discussed later.

TABLE III

Significant Coronary Arterial Narrowing by Age Groups

Age Range (yr)	Patients Studied (no.)	Significant Lesions	
		no.	%
14–19	3	0	0
20–24	11	0	0
25–29	27	5	18
30–34	76	6	8
35–39	168	30	18
40–44	301	76	25
45–49	414	119	29

TABLE IV

Significant Coronary Arterial Lesions and Serum Cholesterol Levels

Serum Cholesterol (mg/100 ml)	Patients Studied (no.)	Significant Lesions	
		no.	%
<200	230	24	10
201–225	161	28	17
226–250	188	41	22
251–275	156	47	30
276–300	87	30	34
301–350	60	25	42
>350	46	29	63

The distribution of significant lesions by the artery or arteries involved (Table I) was strikingly similar to the distribution in the young men and in patients in the unselected series. Single vessel disease was more common than it was in young men or in the unselected group (Table II), and this finding was reflected in the slightly lower average of 1.9 affected arteries per patient.

Age: As expected, significant disease was found more frequently in older patients (Table III). However, the only death in the entire series occurred at cardiac catheterization in the youngest patient, aged 26, who had subtotal occlusion of the left main trunk near its origin. She sustained infarction during catheterization and was immediately taken to surgery. At that time (February 1966), saphenous vein bypass grafting was not being performed, and she died. Her cholesterol level was 300 mg/100 ml. She had taken birth control pills for 7 months after the birth of her baby, but the chest pain had begun during pregnancy. Autopsy studies revealed severe coronary atherosclerosis.

Serum cholesterol: The prevalence of coronary artery disease increased with increasing levels of serum cholesterol (Table IV). Only 10 percent (24 of

TABLE V

Frequency of Significant Narrowing and Total Obstruction of Each Coronary Artery

Severity of Obstruction	RCA		LCA		LAD		LCx	
	Total Patients	Only Artery	Total Patients	Only Artery	Total Patients	Only Artery	Total Patients	Only Artery
Significant narrowing	138	21	25	10	173	60	107	10
Total occlusion	57	43	1	0	47	34	23	14

Abbreviations as in Table I.

TABLE VI

Relation of Number of Coronary Arteries Involved to Duration of Symptoms

	Duration of Symptoms							
	<6 Months		6–12 Months		1–3 Years		>3 Years	
	no.	%	no.	%	no.	%	no.	%
Affected arteries (no.)								
1	29	63	19	46	26	41	26	31
2	7	15	11	27	25	39	24	29
3	10	22	11	27	12	19	29	35
4	0	0	0	0	1	2	4	5
Total patients (no.)	46	...	41	...	64	...	83	...
Total arteries (no.)	73	...	74	...	116	...	177	...
Affected arteries per patient (average no.)	1.6	...	1.8	...	1.8	...	2.1	...

230) of those with values of less than 200 mg/100 ml had significant lesions, whereas 44 percent (84 of 193) of those with values of more than 275 mg/100 ml had such findings.

Location of coronary artery disease: The left anterior descending coronary artery was the artery most frequently involved (Table V), and was affected in 60 percent of cases of single vessel disease. In the group of young men and in the unselected patients, this vessel was also the one most frequently affected. By contrast, although single vessel disease of the left main trunk occurred in none of the young men and in only 3 of the 1,000 unselected patients, it occurred in 10 of the 1,000 women younger than age 50. Bruschke et al.[6] have shown the ominous prognosis of left main coronary arterial lesions.

Total occlusion was most common in the right coronary artery (Table V), as had also been the case in the two other groups. The left main trunk was totally occluded in one woman who also had total occlusion of the right coronary artery within 2 cm of its origin. She had an extensive network of collateral vessels from atrial branches of the right coronary artery. She was 33 years old, menstruating, not taking birth control pills, not a smoker, normotensive, not diabetic, and had a cholesterol level of 292 mg/100 ml. Clinically she had chronic congestive heart failure and exertional chest pain.

Of the 43 patients with total occlusion of only the right coronary artery, 7 had no significant narrowing of any other coronary artery; of 34 with total occlusion of only the left anterior descending coronary artery, 18 had no significant narrowing of another artery; of 14 with total occlusion of only the circumflex branch, 3 had no other significant narrowing.

Arterial involvement and duration of symptoms: With increasing duration of symptoms there was the expected increase in severity of disease as indicated by a reduced frequency of single vessel disease, an increased frequency of two and three vessel disease, and the appearance of four vessel disease (Table VI). This increased severity is further shown by the increase in the average number of arteries involved per patient as the duration of symptoms increased.

This observation is not helpful in making the diagnosis of coronary artery disease, since long duration of symptoms was characteristic of subjects with normal coronary arteries, and may in fact have been an indication for study.

Occurrence of Myocardial Infarction

Electrocardiographic evidence of myocardial infarction: Such evidence was unusual in single vessel disease (Table VII). With less than total occlusion, it was found only in lesions of the left anterior

TABLE VII

Electrocardiographic Evidence of Myocardial Infarction in Subjects with Involvement of One Coronary Artery

Artery	Significant Narrowing Without Total Occlusion		Total Occlusion			
			With Other Significant Narrowing		Without Other Significant Narrowing	
	no. (ratio)	%	no. (ratio)	%	no. (ratio)	%
RCA	0/14	0	7/36	19	1/7	14
LCA	0/10	0	...	...	...	...
LAD	5/42	12	7/16	44	4/18	22
LCx	0/7	0	0/11	0	0/3	0

Abbreviations as in Table I.

TABLE VIII

Correlation of Definite Electrocardiographic Evidence of Myocardial Infarction with Left Ventriculographic Evidence of Impaired Contractility in 83 Patients with Total Occlusion of a Single Coronary Artery*

Artery	Electrocardiographic Evidence of Infarction		No Electrocardiographic Evidence of Infarction	
	With Impairment	Without Impairment	With Impairment	Without Impairment
RCA	8	0	14	14
LAD	11	0	12	10
LCx	0	0	8	6
Total	19	0	34	30

* Excluding six patients (five with total right and one with total left anterior descending coronary occlusion) who did not have ventriculography and two patients with left bundle branch block (both with total right coronary occlusion, one with and one without impaired contractility).

Abbreviations as in Table I.

TABLE IX

Number of Coronary Arteries Involved in Patients with Electrocardiographic Evidence of Myocardial Infarction

Arteries (no.)	Patients (no.)
0	11
1	10
2	9
3	16

descending coronary artery, and in only 12 percent of these. It was even unusual in total obstruction of single vessels, unless there was additional significant involvement of other arteries (Table VII). Even then the incidence was only 44 percent with left anterior descending, 19 percent with right, and none with circumflex coronary arterial obstructions. As noted, one woman did have total occlusion of both the left main and right coronary arteries without electrocardiographic evidence of myocardial infarction.

TABLE X

Correlation of Clinical Diagnoses with Significant Coronary Lesions

Diagnosis	Patients (no.)	Significant Lesions (no.)	Correlation (%)
Normal	80	1	99
Probably normal	501	49	90
Angina			
Atypical	147	38	26
Grades I–III	44	21	48
Grade IV	69	35	51
Coronary failure	90	53	59

Diminished contractility by left ventricular angiography: When performance of left ventriculography became routine in 1963, it was possible to correlate electrocardiographic evidence of myocardial infarction with areas of decreased contractility or aneurysm as shown in Table VIII, which considers patients with total occlusion of a single artery. All the women with electrocardiographically demonstrated infarction had areas of impaired contractility by left ventriculography, but slightly more than half of those without electrocardiographic evidence of infarction also had left ventriculographic evidence of decreased contractility. Similar although less clear-cut findings were reported in the group of young men.[4] In 52 of 60 young men with electrocardiographic evidence of infarction, areas of diminished contractility were revealed by left ventriculography; among those without electrocardiographic evidence of infarction, left ventriculograms revealed areas of decreased contractility in approximately a third (36 of 111). Miller et al.[7] recently reported similar findings in a group of patients with at least 75 percent narrowing of one or more coronary arteries. Of 77 patients with pathologic Q waves, 73 had evidence of dyssynergy on angiography, whereas 11 of 46 without pathologic Q waves had evidence of dyssynergy. Whether the region of diminished contractility represents necrosis or an area of potentially reversible ischemia is unknown.

A significant number of women with total obstruction of a single coronary artery had neither electrocardiographic evidence of infarction nor areas of diminished contractility demonstrated by ventriculography. This group included 39 percent (14 of 36) of those with total occlusion of the right, 30 percent (10 of 33) of those with total occlusion of the anterior descending and 43 percent (6 of 14) of those with total occlusion of the circumflex coronary artery.

Myocardial infarction in absence of coronary artery disease: Of 46 patients with electrocardiographic evidence of myocardial infarction (Table IX), 11 had no significant coronary artery disease. Three of these had primary myocardial disease; one did not have left ventriculography; one was thought on reevaluation to have a variant of the Wolff-Parkinson-White syndrome; two (one with an inferolateral, the other with an inferior myocardial infarction) had unusually large posterior papillary muscles. One patient with an apical aneurysm had complained of fatigue, but never pain. Another with diminished contractility of the diaphragmatic surface of the left ventricle had 30 to 40 percent narrowing of the right coronary artery, a finding that may have represented resolution of an earlier, more severe lesion.[8] The remaining two patients, one with atypical pain, the other with paroxysmal atrial tachycardia, had normal left ventriculograms as well as normal coronary arteries. All 11 were premenopausal, none were taking oral contraceptive agents, none had hypertension and only three had cholesterol levels above 275 mg/100 ml.

Only 6 of the 109 young men with electrocardiographic evidence of myocardial infarction had normal coronary arteries. Two had primary myocardial disease; one had had blunt trauma to the chest; one probably had myocarditis; the fifth did not have a definite myocardial infarction on review of his electrocardiogram; and findings in the sixth patient remained unexplained.

Clinical Correlations

Compared with data in the group of patients unselected by age or sex[1] and in the series of young men,[4] the correlation of clinical diagnoses with arteriographic findings was disappointing (Table X). Although there was excellent correlation when the clinical impression was that the pain was not angina pectoris, only half of those with apparently typical angina had significant coronary artery disease. The correlation was only slightly better with pain at rest and "coronary failure" (pain lasting more than 15 minutes), and only a fourth of those with atypical angina pectoris (pain with unusual or inconstant precipitating factors) had significant coronary artery disease.

In their summary of the hypotheses advanced to explain the cause of "angina-like pain without identifiable cause" Herman et al. included small vessel disease, spasm of the coronary arteries, oxyhemoglobin dissociation defects, misinterpretation of arteriograms, cardiomyopathy and psychosomatic factors. None of these explanations seem entirely adequate. The entity does appear to have a good prognosis, and this fact is a major impetus for the study of patients such as those analyzed in this report.

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Radiation-Related Pericarditis

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To determine the incidence of pericardial effusion in patients undergoing upper mantle radiation therapy, 81 patients with Hodgkin's disease, stages I to IIIB, were selected from a protocol series of 98 patients. Twenty-four patients (29.6 percent) met X-ray criteria for the presence of pericardial effusion. Eleven of the 24 also underwent right heart catheterization to confirm the presence of pericardial effusion and to define any hemodynamic abnormality. Fourteen patients were found to have transient effusion. Five of the 11 patients have had partial pericardiectomy for symptoms and signs of cardiac tamponade. There has been no evidence of recurrent Hodgkin's disease in these surgically treated patients. Ninety-two percent of the pericardial effusions occurred in the first 12 months after the end of radiation therapy. Therapeutic implications depend on elucidation of the natural history of this process. At present close follow-up is necessary with surgical intervention for signs or symptoms of cardiac tamponade.

Early reports[1–4] tended to minimize the effect that radiation therapy may have on the heart. In fact, Vaeth et al.[3] stated, "If cardiac damage is induced by irradiation, it appears to be of such insignificance that modification of adequate present day techniques is not justified." Subsequently, it has been recognized that radiation therapy to portions of the heart can result in damage.[5–7] The cardiac effects may be immediate, as in pericarditis occurring during radiotherapy,[8,9] or the onset of acute pericarditis may be delayed for months to years.[8,9] Chronic asymptomatic effusion may occur[10] and, in some, may progress to tamponade.[8,10,11] There are also reports of myocardial infarction,[8,12] myocarditis,[13] aortitis[6] and valvulitis.[11,14] Either transient or persistent pericardial effusion developed in 24 of 81 patients with Hodgkin's disease, stages I to IIIB, who underwent upper mantle radiation therapy. This paper concerns the clinical recognition and management of these patients.

Materials and Methods

Patients were selected from a protocol series of 98 patients with Hodgkin's disease who were treated and followed up at the Baltimore Cancer Research Center. Thirteen of these patients had stage IV disease and did not receive radiation therapy. One patient died of pneumonia 3 months after radiotherapy, two other patients died of progressive Hodgkin's disease and another patient was lost to follow-up. This left 81 patients with stages I to IIIB in the determinate group. All patients received upper mantle radiation therapy with ^{60}cobalt teletherapy for 22 to 35 days at a total dose of 4,000 rads. The mean mid-plane dose to the heart was 4,623 rads. A more detailed analysis of the radiation therapy is presented elsewhere.[15]

The patients had a complete medical evaluation, including chest X-ray film and electrocardiogram, before radiation therapy. They were reevaluated at monthly intervals for the first 3 months, at 3 month intervals for the next year, at 6 month intervals the following year, and annually thereafter unless the disease recurred: Chest X-ray films from these serial follow-up studies

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were evaluated for enlargement of the cardiac silhouette. Pericardial fluid was considered present if there was a distinct change in cardiac configuration or if the transverse cardiac diameter was more than 1.5 cm greater than that on the chest X-ray films obtained before radiation therapy. These criteria have been used by others[10] and, as recommended by them, care was taken to use preradiation therapy X-ray films as the base line.

Records were reviewed of patients who met the X-ray criteria for pericardial effusion. Serial electrocardiograms were reviewed with particular attention paid to voltage and ST-T wave changes. Patients who manifested a persistent increase in transverse cardiac diameter at the time of the study were reevaluated for evidence of symptoms and signs of pericarditis or tamponade, or both.

Eleven patients underwent right heart catheterization. Pressures were recorded from the pulmonary capillary wedge position, main pulmonary artery, right ventricle and right atrium. Cardiac output was determined by injection of indocyanine green dye into the main pulmonary artery and sampling from a left brachial arterial needle. Levophase left ventricular cineangiograms were obtained in the right anterior oblique projection after injection of contrast medium into the main pulmonary artery. Left ventricular volume data were calculated using the single plane method.[16] Right atrial anteroposterior cineangiograms were also obtained to confirm the presence of fluid. Echocardiography was performed in every patient thought to have pericardial fluid at the time of the study. Pericardial fluid was diagnosed according to the criteria of Feigenbaum.[17]

Results

Incidence of pericardial effusion: In the determinate group of 81 patients, 24 (29.6 percent) met the X-ray criteria for the presence of pericardial fluid. In 19 of the 24 there was an increase of more than 1.5 cm over base line in the transverse cardiac diameter, and in 5 patients there was a distinct change in the cardiac configuration without such an increase. Of the five patients with configurational changes only, two had effusion confirmed by catheterization and one additional patient had symptoms of acute pericarditis.

Transient effusion: We found it convenient to consider these patients in two separate groups on the basis of persistence or resolution of pericardial effusion at the time of the study. In 14 patients transient effusions were found during retrospective review of chest X-ray films. These patients are now asymptomatic, have normal cardiac size and configuration on chest X-ray studies, and have no evidence of constrictive pericarditis. They were usually asymptomatic at the time of study, and the diagnosis of pericardial effusion was made in most cases retrospectively. Two patients underwent catheterization to confirm their hemodynamic status and were followed up clinically and with echocardiograms; the effusion in both of these patients has resolved. A third patient in this group has had repeated episodes of acute pericarditis confirmed by electrocardiographic changes and the presence of a pericardial rub. Results of collagen, vascular and viral studies have been normal. There has been no evidence of pericardial fluid by echocardiogram in this patient.

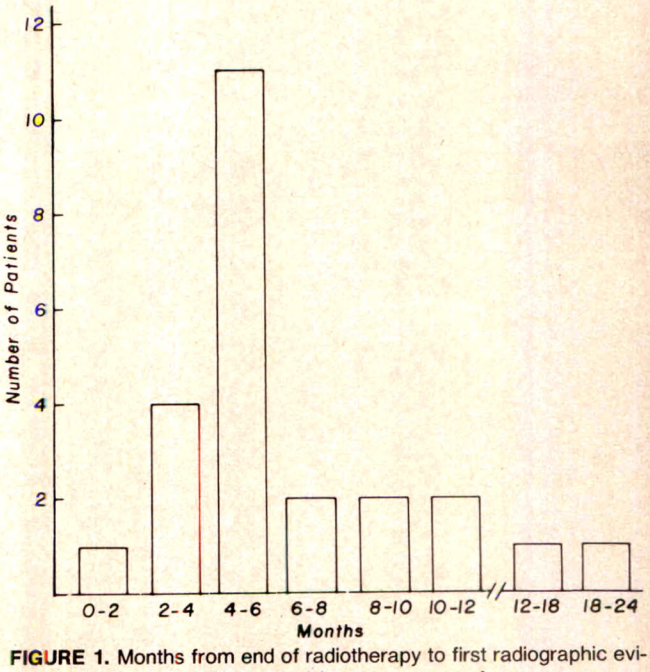

FIGURE 1. Months from end of radiotherapy to first radiographic evidence of pericardial effusion in 24 cases.

Persistent effusion: Ten patients had persistent effusion. The most common symptom was dyspnea on exertion, with 9 of 10 patients complaining of this symptom to some degree. Three patients had fever and four had chest pain. However, none of these 10 patients had a definite pericardial friction rub. Three patients had physical signs of pericardial tamponade with a positive Kussmaul's sign and paradoxical pulse. One patient, initially free of symptoms, has died from recurrent intrathoracic Hodgkin's disease; it is difficult to compare his findings with those of the rest of the group.

Figure 1 shows the time course from the end of radiation therapy to the onset of pericardial effusion in both groups. Ninety-two percent of the pericardial effusions occurred in the first 12 months after the end of radiation therapy, with 42 percent occurring 4 to 6 months after termination of therapy. In two patients effusions developed as late as 16 to 23 months after discontinuation of radiation therapy.

Electrocardiograms: Table I shows the electrocardiographic data from both groups. The electrocardiogram was not helpful in detecting patients with transient effusion but was very useful in patients with persistent effusion. The criteria for low voltage[18] were met in 6 of 10 patients, and 5 of these later underwent pericardiectomy. Two of the 10 had a significant drop in QRS voltage that was not sufficient to meet the standard criteria for low voltage. Therefore, in 8 of 10 patients voltage changes in the electrocardiogram were helpful in the diagnosis of significant pericardial effusion. No arrhythmias were noted, and ST-T changes were not significant.

Echocardiograms: In all 10 patients with persistent effusion and in 2 patients with transient effusion, echocardiograms were obtained and were posi-

TABLE I

Electrocardiographic Changes in Radiation-Related Pericarditis

	Patients (no.)	QRS Voltage		Non-specific ST-T Wave Changes
		Low*	Change†	
Transient effusion	14	0	1	1
Persistent effusion	10	6	2	7

* Low QRS voltage defined by limb lead R or S wave less than 5 mm and precordial R or S wave less than 8 mm.[18]

† QRS voltage change defined as a change from prior electrocardiograms but not meeting criteria for low QRS voltage.

tive for pericardial effusion. The echocardiogram was useful in following up these patients and confirmed the disappearance of the fluid in the two patients with transient effusion as the chest X-ray film showed the transverse cardiac diameter returning to base line.

Cardiac catheterization: Eleven patients underwent right heart catheterization. Three patients had intracardiac pressures consistent with tamponade and underwent partial pericardiectomy within 3 weeks after the catheterization. Two additional patients without catheterization evidence for tamponade underwent pericardiectomy 53 and 109 days, respectively, after catheterization when symptoms progressed and were compatible with early tamponade. A repeat catheterization was not performed before pericardiectomy in these two patients since the symptoms and signs were thought to be typical of tamponade. In two patients intracardiac pressure measurements and cardiac output determinations were made after exercise to help elucidate the hemodynamic significance of the pericardial fluid. In both cases the measurements obtained after exercise were normal. Angiographic volume data revealed low normal left ventricular volume in most cases, and high normal ejection fractions.

Pericardiocentesis: This procedure was performed in two patients. The fluid was straw-colored and contained 6.0 and 5.2 g/100 ml protein, respectively, with 300 to 800 white blood cells, predominantly lymphocytes. Results of cytology and cultures for bacteria, fungi and mycobacteria were negative.

Figure 2A shows the postpericardiocentesis chest X-ray film in Case 3 after air had been instilled into the pericardial sac. The pericardium is very thin. Very rapid reaccumulation of the fluid ensued (Fig. 2B).

Surgical findings: Partial pericardiectomy through a left thoracotomy was performed in five patients. The parietal pericardium was described as mildly to moderately thickened over the anterior surface with dense adhesions to the posterior surface of the sternum. There was a mild visceral pericardial reaction over the right atrium and right ventricle. The left ventricle and the overlying pericardium appeared not to be involved in any inflammatory reaction. There was no evidence of recurrent Hodgkin's disease grossly at the time of surgery or histologically in the excised pericardium. These five patients are now asymptomatic and have normal transverse cardiac diameter on X-ray film and normal voltage on electrocardiograms.

Discussion

Postradiation pericardial effusion: Serial evaluation of chest X-ray films in this study revealed a substantial percentage of patients with pericardial effusion related to radiation therapy. Many of the pa-

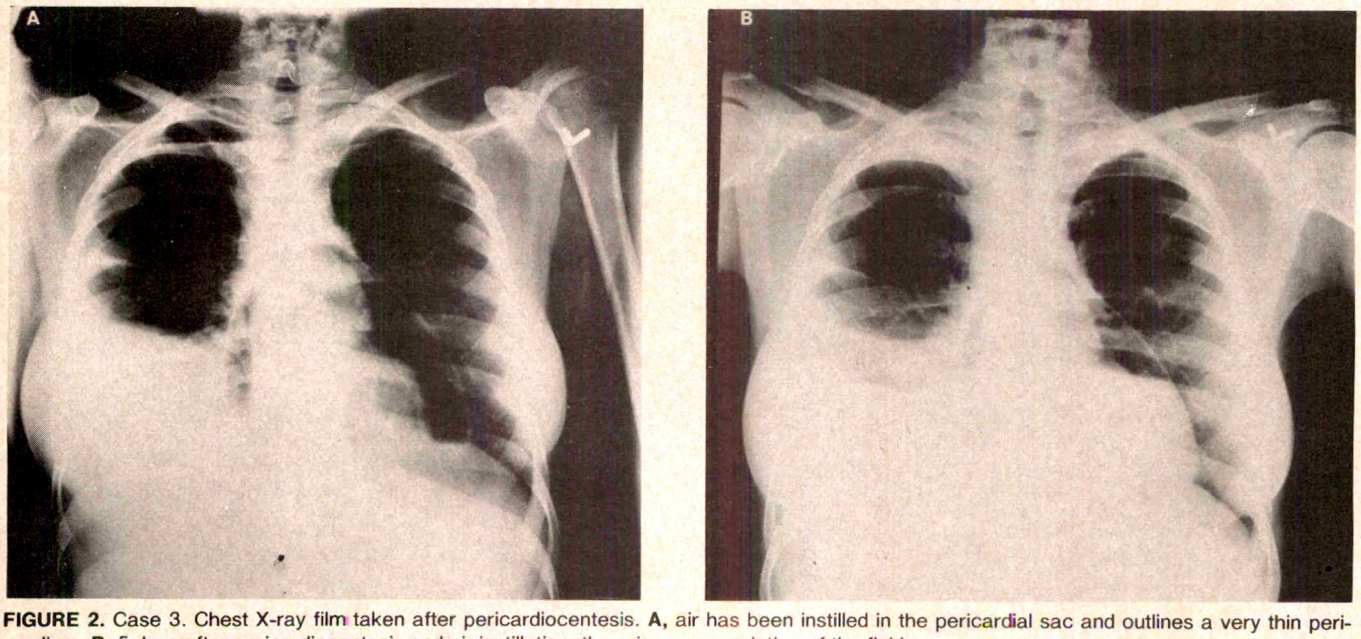

FIGURE 2. Case 3. Chest X-ray film taken after pericardiocentesis. **A,** air has been instilled in the pericardial sac and outlines a very thin pericardium. **B,** 5 days after pericardiocentesis and air instillation, there is reaccumulation of the fluid.

tients with transient effusion were asymptomatic and the disorder would not have been diagnosed without frequent serial chest X-ray studies. Cohn et al.[8] noted that pericarditis developed in 6 percent of their patients with Hodgkin's disease and upper mantle radiation therapy. Our incidence of 29.6 percent is more consistent with the 25 percent incidence reported by Morton et al.[19]

Our patients were, in part, studied by retrospective analysis of chart-recorded incidence of symptoms and signs of acute pericarditis. It is well known[20,21] that the diagnosis of acute pericarditis may be difficult, and many of the subtle complaints of fleeting chest pain, cough or fever noted during and shortly after radiation therapy may represent acute pericarditis without significant effusion.

Steinberg[22] has noted that at least 250 cc of fluid in the pericardial sac is necessary to cause recognizable changes in the cardiac shadow on X-ray examination. Therefore, separation of patients by his technique may also underestimate the number of patients with pericardial reactions secondary to radiation therapy. Although we did not have the opportunity to obtain echocardiograms routinely in all of these patients, the addition of echocardiography should be very helpful in detecting early asymptomatic pericardial effusions and should prove useful in following up these patients.

Pericardial fluid analyzed by us and others[7,8,11,23] has consistently shown a high protein content and a predominance of lymphocytes. The fluid may be serous or serosanguineous.

Role of pericardiocentesis: The pericardium in patients with radiation-related pericarditis has been described as moderately thickened by fibrosis with minimal inflammatory reaction at surgery or autopsy.[19,23] Pericardial air study has also revealed a thick pericardium.[8] In our patients the pericardium was thin with a mild to moderate fibrotic reaction anteriorly. Pericardiocentesis in one patient revealed a thin pericardium when air was instilled, and rapid reaccumulation of the fluid occurred. Other reports[19] have also demonstrated rapid reaccumulation of the fluid. Therefore this procedure has limited therapeutic benefit unless there are symptoms or signs of tamponade and time is needed to prepare for surgery. Morton et al.[19] have suggested that pericardiocentesis be performed before surgery in patients with tamponade. They believe that this procedure may prevent circulatory collapse during induction of anesthesia when right heart filling pressure decreases because of vasodilatation. The diagnostic benefit from pericardiocentesis also seems limited. Certainly Hodgkin's disease is difficult to diagnose from cytologic examination[24] although tuberculosis and fungal cultures are useful.

Prognosis: The natural history of the pericardial effusions following radiation therapy is variable. Some effusions, as in our group, may be transient with no ill effects at least on short-term follow-up studies. Only time will tell whether any of these patients will manifest late problems with cardiac constriction. The time for disappearance of the fluid is variable; it ranged from 1 to 16 months in our group and from 2 to 17 months in the group described by Pierce et al.[10] We therefore recommend that patients with small asymptomatic effusions be followed up clinically as well as by chest X-ray films, electrocardiograms, and echocardiograms.

Large persistent effusions present a somewhat more difficult problem. Some effusions, although initially asymptomatic, may progress to tamponade. Indeed, Morton et al.[19] believed that tamponade contributed to the death of 6 of 27 patients with radiation-induced pericarditis. It is of utmost importance to recognize that such effusion can occur and may progress. Otherwise the condition may be diagnosed as recurrent Hodgkin's disease and aggravated by further radiation therapy.

It is difficult to decide when to recommend elective pericardiectomy. Morton et al.[19] recommended surgery for all symptomatic patients and for asymptomatic patients who had a 5 cm increase in transverse cardiac diameter persisting for 6 to 9 months. Serpick[24] and Roberts et al.[25] have pointed out that surgery might be preferred not only for hemodynamic problems but also to exclude recurrent Hodgkin's disease.

There is concern about the late development of constrictive pericarditis in patients with acute radiation-related pericarditis. Several reports have demonstrated that constrictive pericarditis may follow cardiac irradiation.[8,26,27] Muggia and Cassileth[28] described a patient with an esophageal carcinoma who, 9 months after radiation therapy, had acute pericarditis with effusion that progressed to constrictive pericarditis 2 months later. Steinberg[14] reported an effusive constrictive pericarditis occurring 3 and 20 years after radiation therapy for left breast carcinoma. Haas[29] reported constrictive pericarditis occurring 45 years after radiation to the mediastinum.

Treatment: We now recommend that patients with increased transverse cardiac diameter who are asymptomatic be followed up clinically, and with echocardiograms. There is a suggestion that some of these large effusions may gradually disappear, as noted by Morton et al.[19] in three patients followed up for 42 to 50 months and as we found in two patients followed up for 18 and 22 months, respectively. Patients who manifest symptoms on follow-up study should undergo right heart catheterization to substantiate the presence of pericardial tamponade. If right heart pressures at rest are found to be normal, we continue to follow up these patients without recommending pericardiectomy. If resting pressures are increased, suggesting hemodynamic abnormalities resulting from pericardial fluid, pericardiectomy is recommended. As part of the catheterization evaluation, a levophase left ventriculogram is obtained both to confirm the effusion and to document that left ventricular volume and function are normal. There are reports of radiation-induced myocarditis and heart

failure,[13] and of radiation-induced myocardial fibrosis simulating constrictive pericarditis.[30]

Further prospective study is needed to confirm the incidence of acute transient pericardial reactions. The echocardiogram should prove useful in this regard, but careful attention to symptoms and signs of acute pericarditis is also needed in these patients. Recognition of the problem of chronic pericardial effusion with the possibility of development of cardiac tamponade is stressed so that treatment of a reversible life-threatening illness will not be overlooked. The precise mechanism responsible for the radiation-induced effusions remains obscure. It is possible that change in radiotherapeutic techniques may reduce the incidence of pericardial effusion.

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Symposium on the Effects of Surgical Treatment on the Natural History of Acquired Heart Disease. Part II. Aortic and Mitral Valve Disease

JOHN ROSS, Jr., MD, FACC, *Guest Editor*

Natural History of Aortic and Mitral Valve Disease

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An appreciation of the natural history of acquired valvular heart disease is a prerequisite to an understanding of how surgical intervention has altered the natural outlook. The prognosis for a patient with valvular heart disease treated medically is dependent on the stage of the disease at which he is first seen. Therefore, assessment for surgery requires evaluation of the pathophysiologic consequences that have resulted from the hemodynamic alterations. Survival statistics for patients seen at the University of California Medical Center at San Francisco are presented and compared with the data of others. Stenotic lesions appear to have a poorer prognosis than chronic regurgitant lesions and generally warrant surgical intervention at an earlier functional stage of the disease. However, valvular insufficiency produced acutely is poorly tolerated and may constitute a surgical emergency.

The selection of patients with mitral or aortic valve disease for surgery obviously requires an appreciation of the natural history of valvular heart disease. One must weigh the expected surgical morbidity and mortality against the anticipated outcome of medical management alone. Therefore, one must know not only the early and late results of surgical procedures for various valvular lesions, but also the pathophysiologic consequences of valvular heart disease at various stages in its natural history. Simple awareness of average survival statistics is inadequate. For example, the prognosis of asymptomatic mitral stenosis differs greatly from that of mitral stenosis that has led to severe pulmonary vascular disease with resultant pulmonary hypertension and cardiac decompensation. The purpose of this review is to examine the major valvular lesions in terms of their pathophysiologic consequences and their natural history in the absence of surgical intervention.

Mitral Stenosis

Figure 1 illustrates diagrammatically the hemodynamic consequences of mitral stenosis at various stages of the disease. As a result of acute rheumatic fever, gradual fibrosis occurs and involves the valvular commissures. Bland and Jones,[1] who studied 1,000 children for 20 years after acute rheumatic fever, reported that nearly two thirds of those who ultimately had mitral stenosis had no clinical evidence of the disease 10 years after the onset of rheumatic fever. During the next 10 years on the average the diagnosis can be made clinically but the patient is asymptomatic. Thus, the average patient is in the fourth decade of life when the stenosis becomes hemodynamically significant, that is, when the mitral orifice is reduced to approximately 1.5 to 2.5 cm^2 (normal 4 to 6 cm^2). At this point, the fibrotic mitral valve begins to obstruct the flow of blood when cardiac output in-

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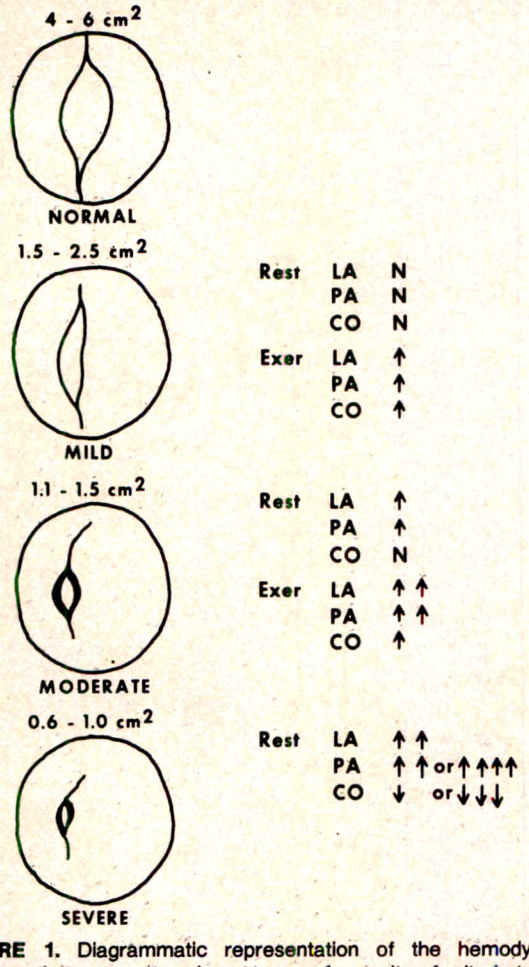

FIGURE 1. Diagrammatic representation of the hemodynamic changes that occur at various stages of severity of mitral stenosis. The valve area is listed above each stage. ↓ = decreased; ↑ = increased; CO = cardiac output; Exer = exercise; LA = left atrial pressure; N = normal; PA = pulmonary arterial pressure.

creases and the diastolic filling period per minute decreases during exercise; consequently, left atrial and pulmonary capillary pressures increase and the patient first experiences shortness of breath with exertion. Eventually, over the next 10 years or so, the orifice is reduced to an area of 1.1 to 1.5 cm^2, and flow is now effectively obstructed even when the patient is resting. At this point the patient is likely to experience significant pulmonary congestive complaints such as orthopnea, nocturnal cough, paroxysmal nocturnal dyspnea, hemoptysis and dyspnea on minimal exertion. As the orifice finally decreases to less than 1 cm^2, the chronically increased pulmonary venous and capillary pressures frequently lead to the development of significant pulmonary vascular disease. Pulmonary arterial pressure increases out of proportion to the increase in pulmonary capillary pressure; there is also a marked reduction in cardiac output. Right ventricular failure and death follow shortly. The average age at death of patients with mital stenosis treated medically is about 48 years.[2]

Natural history of surgically untreated mitral stenosis: Sujoy and Gopinath[3] recently summarized the natural history of surgically untreated mitral stenosis in three large series of patients: Olesen and Baden's series[4] of 271 patients treated in the presurgical era between 1933 and 1949, Rowe and associates' group[5] of 250 patients seen initially between 1925 and 1947, and Wilson and Lim's series[6] of 269 patients with auscultatory evidence of mitral stenosis and insufficiency in which age 20 was considered the year of onset of mitral stenosis. The survival figures differ strikingly. Whereas 66 percent of Olesen and Baden's patients died within 10 years of diagnosis, only 7 percent of Wilson and Lim's patients died during the same number of years. It is clear from the published studies that when one examines a series of patients with mitral stenosis at different stages of the disease, the ultimate survival figures are highly dependent upon whether the patients are first seen in an asymptomatic or latent stage (as in most of Wilson and Lim's cases) or in the later symptomatic stage.

Olesen and Baden's study is particularly useful since the patients were classified according to various functional categories. Their patients in New York Heart Association functional class III (the authors' class B and C cases) had survival rates of 62 percent 5 years after diagnosis and approximately 38 percent 10 years after diagnosis, whereas class IV patients had only a 15 percent survival rate at 5 years and no survival after 8 years. Figure 2 illustrates our experience with a group of patients followed up over the past 20 years at the University of California, San Francisco. These cases represent an unselected mix of all stages of pure mitral stenosis in which the diag-

TABLE I

Causes and Antecedent Conditions of Mitral Insufficiency

I. Acute mitral insufficiency
  A. Ruptured chordae tendineae
    1. Bacterial endocarditis
    2. Trauma
    3. Postmyocardial infarction
    4. Idiopathic
  B. Papillary muscle disease
    1. Rupture postmyocardial infarction
    2. Dysfunction due to ischemic disease
  C. Valvular damage
    1. Leaflet perforation or avulsion due to bacterial endocarditis
    2. Postoperative complications of cardiac surgery
    3. Functional (dilatation)
II. Chronic mitral insufficiency
  A. Rheumatic heart disease
  B. Collagen disorders
  C. Congenital or hereditary disorders
    1. Marfan's syndrome
    2. Myxomatous transformation (floppy valve)
    3. Endocardial cushion defects
    4. Single papillary muscle with parachute valve
  D. Idiopathic hypertrophic subaortic stenosis
  E. Tumor
  F. Myocardial failure
  G. Annular calcification

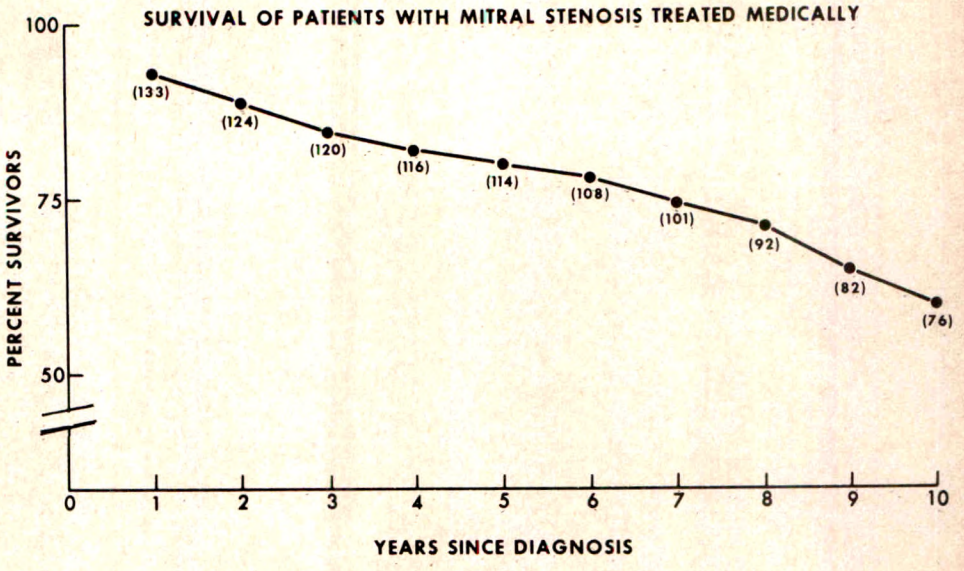

FIGURE 2. Percent survival of patients with medically treated mitral stenosis followed up at the University of California, San Francisco. In this and all subsequent figures, the numbers in parentheses indicate the number of patients known to be dead or alive at that point; the percent survival figures have been corrected accordingly to reflect the actual number of patients in the series at that time.

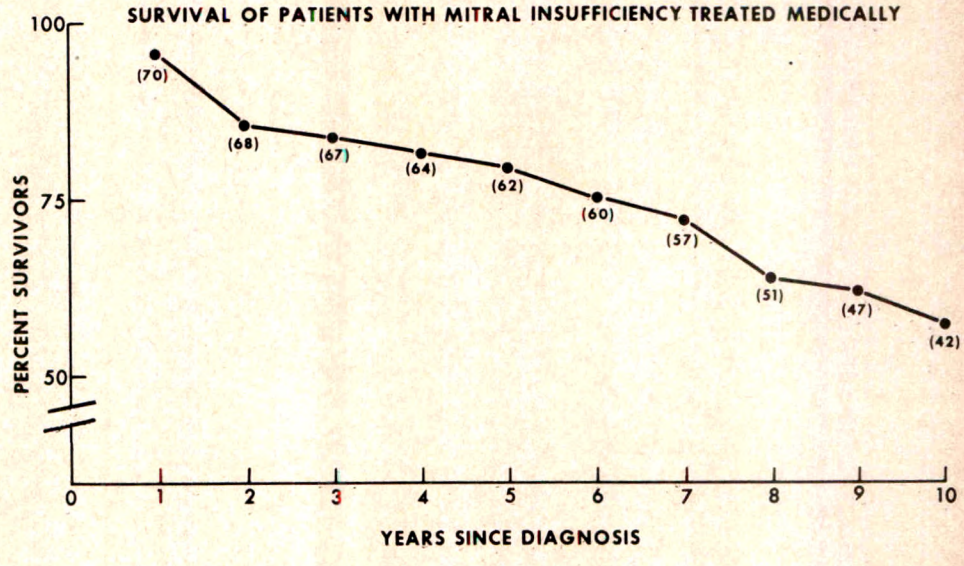

FIGURE 3. Percent survival of patients at the University of California, San Francisco, with medically treated pure mitral insufficiency.

nosis was first made by us or the date of an earlier diagnosis elsewhere could be clearly established. It can be seen from our statistics that in a random series of patients with mitral stenosis diagnosed initially at different stages of the disease, 80 percent are alive after 5 years and approximately 60 percent are alive after 10 years.

Surgical implications: It would appear that a patient with mitral stenosis who is asymptomatic or minimally symptomatic frequently remains so for 10 to 20 years. It is also clear that once the patient becomes seriously symptomatic with mitral stenosis, continuous progression of the disease to death is usually relatively rapid. Thus, it is our general working rule that the asymptomatic patient (functional class I) with mitral stenosis is not a candidate for surgery and that patients in classes III and IV are clearly in need of surgical treatment. The difficult decision of surgical intervention generally occurs in the class II patient: The degree of disability must be carefully evaluated and the particular circumstances of that patient must be individually weighed in reaching a decision regarding surgery.

Mitral Insufficiency

Table I summarizes the more common causes and antecedent conditions of both acute and chronic mitral insufficiency. Since the natural history of acute mitral insufficiency is usually dramatically different from that of the chronic form of the disease, distinction between the two is important. Causes of the acute condition include rupture of the chordae tendineae or of the papillary muscle and actual perforation or avulsion of the valve, which generally occur as a result of acute myocardial infarction, bacterial endocarditis or trauma or as a postoperative complication of cardiac surgery. Although one tends to equate chronic mitral insufficiency with rheumatic heart disease, there are many other causes, including collagen disorders and congenital or hereditary disorders such

as Marfan's syndrome, the floppy valve syndrome, endocardial cushion defects or a single papillary muscle with a parachute valve (Table I).

Acute mitral insufficiency: Acute distension of the left ventricle with resultant thinning of the left ventricular myocardium and the lack of sufficient time to permit compensatory ventricular hypertrophy to develop result in increased stress on the left ventricular wall. Consequently, severe left ventricular failure characteristically occurs with acute mitral insufficiency, resulting in peripheral vascular collapse or acute pulmonary edema, or both. The prognosis for patients with these symptoms is generally poor. For example, at San Francisco General Hospital only two patients survived among nine presenting with either mitral or aortic regurgitation after acute bacterial endocarditis. Acute mitral insufficiency can produce death within a matter of days in contrast to chronic mitral insufficiency, which can be present for many years with little progression of symptoms.

Chronic mitral regurgitation: A key feature in the gradual development of mitral insufficiency is the apparent increase in left ventricular diastolic compliance, which occurs as the ventricle enlarges in response to the increasing degree of mitral insufficiency. Thus, the Frank-Starling mechanism permits the ventricle to expel a large stroke output, namely, the sum of the regurgitant and the forward stroke output, through an increase in end-diastolic volume. However, this increase in end-diastolic fiber length is not reflected in augmented end-diastolic pressures because of the increase in left ventricular compliance with time. Consequently, severe pulmonary capillary hypertension is avoided and the patient remains free of incapacitating pulmonary congestive symptoms.

An additional important factor that permits the patient with chronic mitral insufficiency to survive for many years, often with surprisingly little disability, is the unloading of the left ventricle during systole. There is no isovolumetric contraction since regurgitation begins immediately with the onset of systole. This unloading protects the ventricle by preventing development of an undue degree of tension within its walls, permitting the energy of contraction to be expended in useful shortening. It is of interest that mitral insufficiency in the experimental animal does not increase myocardial oxygen consumption.

Natural history of surgically untreated mitral insufficiency: Our survival statistics for patients with mitral insufficiency who were treated medically at the University of California, San Francisco, are illustrated in Figure 3. Although the condition of these patients was generally first diagnosed at a later stage of the disease than that of our patients with mitral stenosis, the survival statistics are similar; that is, approximately 80 percent of the patients were alive 5 years after the diagnosis of mitral insufficiency was first established, and almost 60 percent were alive 10 years after the diagnosis.

A significant number of patients with rheumatic mitral insufficiency have combined mitral insufficiency and stenosis. Such patients frequently have an orifice area of approximately 2 cm^2 which, in the presence of a normal mitral valve flow, would not require a diastolic pressure gradient with resultant left atrial hypertension. However, in the presence of mitral insufficiency significant left atrial hypertension develops because the large regurgitant volume plus the stroke volume must flow across the somewhat narrowed valvular orifice in diastole. The valve is frequently heavily calcified and relatively fixed, neither closing much in systole nor opening much during

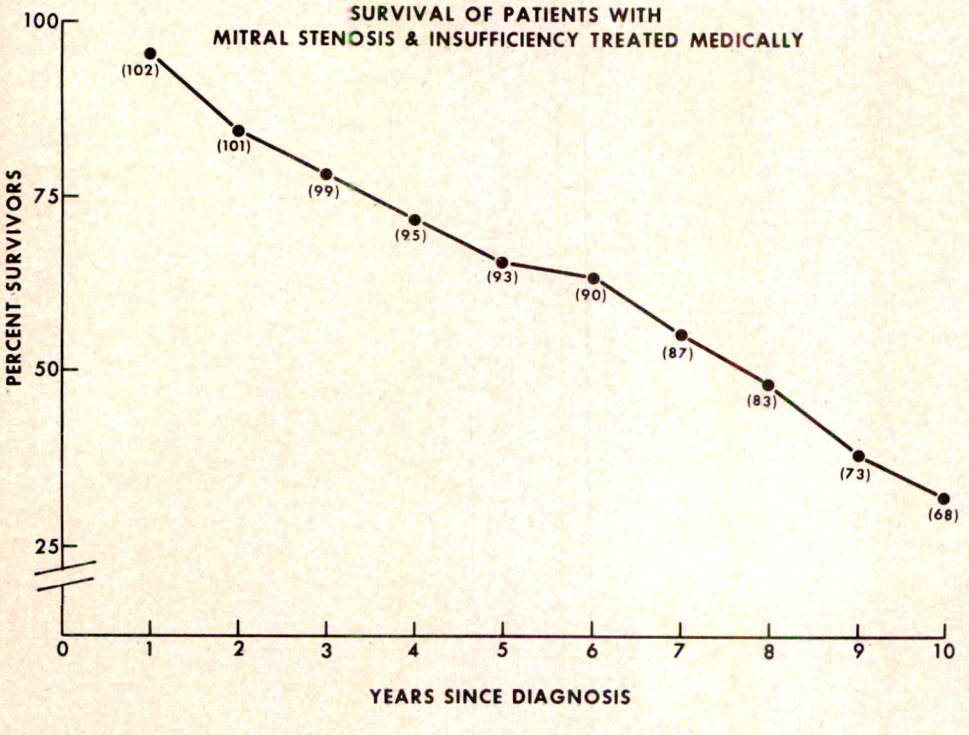

FIGURE 4. Percent survival of patients with combined mitral stenosis and insufficiency treated medically. The prognosis in these patients is worse than that in patients with mitral stenosis alone.

diastole. Left atrial pressure is often comparable to that recorded in patients with pure mitral stenosis.

Surgical implication in combined mitral stenosis and insufficiency: Figure 4 shows the survival statistics of patients treated only medically at our institution after the initial diagnosis of combined mitral stenosis and insufficiency. In contrast to the survival rates for patients with pure mitral stenosis or pure mitral insufficiency, this group had a distinctly worse prognosis. Thus, only two thirds of our patients were alive 5 years and only one third were alive 10 years after the initial diagnosis. Prosthetic valve replacement is almost always necessary in these patients and is recommended despite its hazards whenever evidence of significant hemodynamic impairment is present because of the poor prognosis with medical management.

Aortic Insufficiency

Acute aortic insufficiency: The natural history of acute aortic insufficiency also differs from that of chronic aortic insufficiency. The sudden volume load placed on the left ventricle results in an increase in wall tension in accordance with the Laplace law. The left ventricle, dilated by the sudden increase in volume without compensatory hypertrophy, has a systolic stress upon its wall that is much greater than normal and leads rapidly to left ventricular failure. The patient presenting with sudden left ventricular failure and apparent wide open aortic insufficiency usually has clear-cut clinical findings, and medical therapy is frequently associated with a high rate of mortality, often within hours to days. We consider that these patients should be treated as candidates for emergency surgery.

Chronic aortic insufficiency: In striking contrast, aortic regurgitation that develops chronically and progressively generally has a protracted course, causing little disability for many years. Although the volume of regurgitation may eventually be as much as 80 percent of the total stroke output, the ventricle usually is able to put out the large ejection fraction without a large increase in left ventricular end-diastolic pressure, again presumably because of an increase in left ventricular diastolic compliance as the ventricle gradually enlarges over a period of years. Because there is also chronic peripheral vasodilatation reducing aortic impedance, the ventricle is able to perform this increased volumetric work for many years without serious circulatory impairment. Additionally, the hypertrophy that develops as regurgitation develops keeps ventricular stress within the normal range. Ultimately, however, cardiac decompensation ensues.

Patients with aortic regurgitation tend to be free of serious cardiovascular symptoms until relatively late in the course of the disease. Aside from mild dyspnea upon exertion, most patients may be totally free of cardiorespiratory complaints until clear-cut left ventricular failure ensues followed shortly by congestive heart failure. Similarly, angina pectoris generally occurs late in the course of the disease and only in association with severe aortic insufficiency.

Survival in medically treated aortic insufficiency: The survival rate of our patients after chronic aortic insufficiency was diagnosed is depicted in Figure 5. Three fourths of these patients with so-called free or hemodynamically significant aortic insufficiency who were treated medically are alive 5 years and half are still alive 10 years after diagnosis. These data are in good agreement with other reported data[7] suggesting that free or moderate to severe aortic insufficiency has a relatively good prognosis with a general 10 year survival rate of approximately 50 percent. Even more favorable is the 10 year survival rate of 85 to 95 percent for patients with slight to moderate aortic insufficiency[8]; thus, this lesion when mild tends to be well tolerated by the ventricle.

Surgical implications: Once aortic insufficiency progresses to cardiac decompensation, the patient's condition usually deteriorates rapidly. Most patients die within 2 years after the onset of congestive heart

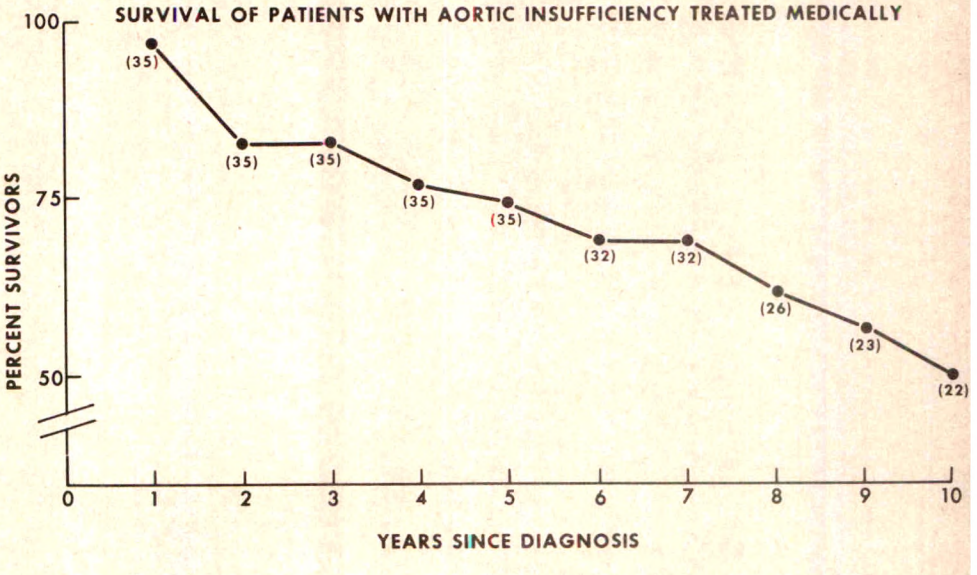

FIGURE 5. Percent survival of patients with aortic insufficiency treated medically and followed up at the University of California, San Francisco.

failure.[9] The average survival rate after the onset of angina pectoris is approximately 5 years.[7] It is clear that once symptoms of heart failure or angina pectoris develop in a patient with aortic insufficiency, surgery should be considered because of the worsened prognosis. On the other hand, the excellent survival rate for many years of patients with even moderate to severe free aortic insufficiency seemingly does not justify early surgical intervention in the asymptomatic patient in view of the mortality and morbidity associated with valve replacement. It is important that the physician be alert to the onset of symptoms in the patient with aortic insufficiency since, once a course of heart failure begins, the surgical survival rate decreases and the results of the operation are not as satisfactory as when surgical intervention is undertaken earlier. Ideally, surgery should be performed as the patient's condition clearly begins to deteriorate with distinct progression of his symptoms but before development of congestive heart failure.

Aortic Stenosis

The overwhelming majority of older patients with isolated aortic stenosis have a congenitally bicuspid aortic valve that has, over the years, secondarily calcified and ultimately obstructed the flow of blood from the left ventricle to the aorta. Presumably, the inability of a bicuspid valve to open fully results in a stretching of the free edges across the aortic orifice during systolic ejection with resultant rapid vibration of the leaflets. This constant trauma leads eventually to thickening, fibrosis and fusion and, ultimately, calcification of the valvular leaflets. There is a positive correlation between the age of the patient and the severity of the valvular obstruction as reflected in the systolic pressure gradient across the aortic valve at the time of cardiac catheterization.[10] Since cardiac output tends to diminish with age, this increase in the systolic pressure gradient strongly suggests that increasing calcification of the valve over the years leads to increasing degrees of obstruction of the aortic orifice and resultant increases in the severity of the stenosis.

Reduction of the aortic orifice from its normal 2 to 4 cm^2 to an area less than 1 cm^2, whether it is due to a calcified bicuspid valve or to rheumatic heart disease, leads to a progressive increase in left ventricular systolic pressure as cardiac output is maintained to meet peripheral metabolic needs. This pressure can reach extremely high levels. We have observed a systolic

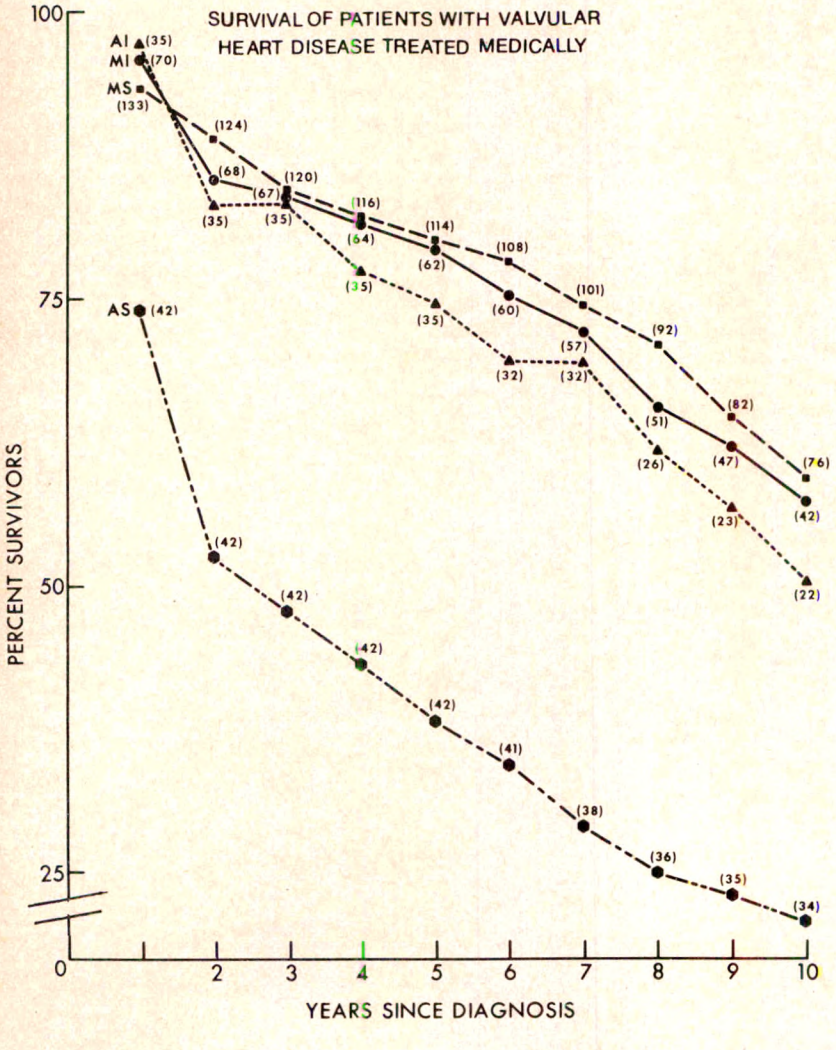

FIGURE 6. Percent survival of patients with valvular heart disease treated medically. The poor prognosis of patients with aortic stenosis (AS) is readily contrasted with findings in patients with aortic insufficiency (AI), mitral insufficiency (MI) and mitral stenosis (MS).

pressure gradient of more than 150 mm Hg across the aortic valve that resulted in a left ventricular peak systolic pressure of approximately 300 mm Hg. Despite this enormous increase in systolic pressure, overall heart size may be enlarged surprisingly little despite marked left ventricular wall hypertrophy; in fact, cavitary volume can even be reduced if heart failure has not ensued. Adequate end-diastolic stretch of the hypertrophied ventricle with its reduced diastolic compliance is accomplished by an increase in the force of the left atrial contraction. The left ventricular end-diastolic pressure achieved as a result of the *A* wave frequently causes an end-diastolic pressure that is much greater than mean left atrial and pulmonary capillary pressures. Thus, a mechanism is provided to effect an increased end-diastolic stretch to the left ventricle without chronic elevation in pulmonary capillary pressures and resultant pulmonary congestive phenomena.

Thus, the patient with tight aortic stenosis, in contrast to the patient with tight mitral stenosis, may be entirely asymptomatic at a time when he has a severe obstruction at the aortic valve. Furthermore, this asymptomatic state may persist for a number of years despite tight aortic stenosis, particularly when the lesion is congenital. Eventually, however, as both peripheral and central adaptive responses fail to maintain adequate delivery of blood flow to the peripheral tissues, mean left atrial and pulmonary capillary pressures increase, initially only with exercise but eventually during rest, as clear-cut left ventricular failure ensues. Thus, although pulmonary arterial and capillary pressures are normal in the majority of patients with isolated aortic stenosis who undergo cardiac catheterization, some patients do have elevated left atrial and pulmonary arterial pressures that ultimately lead to the syndrome of congestive heart failure.

Survival rates of medically treated patients with aortic stenosis: surgical implications: Although the asymptomatic patient with hemodynamically significant aortic stenosis may survive for many years until he becomes symptomatic, two points deserve emphasis. First, such patients are candidates for sudden death. Although such deaths occur only occasionally and are presumably due to arrhythmia rather than hemodynamic complications, they occur in patients with all types of aortic stenosis, including children with congenital stenosis and adults with an acquired lesion, particularly when the lesion is hemodynamically severe. This is one of the major reasons why we recommend surgical relief of the obstruction once severe hemodynamic impairment is detected even though the patient is asymptomatic. Second, once symptoms resulting from aortic stenosis develop, the outlook changes dramatically, regardless of whether the symptoms are those of angina pectoris reflecting coronary insufficiency, exertional syncope from cerebral insufficiency, or cardiac decompensation. In reviews of large clinical series of adult patients with aortic stenosis,[7] the average age at the time of clinical presentation is about 48 years whereas the age at death is about 63 years. In contrast, the average survival rate of patients after symptoms appear is less than 5 years in patients with aortic stenosis.[11] Further breakdown according to the various symptoms reveals an average survival rate of 1 1/2 to 3 years for patients with angina, syncope, dyspnea or congestive heart failure. Recently, Frank et al.[11] reported on the follow-up of 15 adult patients with proved hemodynamically significant valvular aortic stenosis who were treated medically: 52 percent died within 5 years and 90 percent within 10 years of diagnosis.

Figure 6 presents the survival statistics at the University of California, San Francisco, for an unselected group of patients with aortic stenosis who were treated medically; the survival rates for the other isolated valvular lesions are superimposed. The considerably more serious prognosis for the patient with aortic stenosis is clearly illustrated. At our institution only 38 percent of the patients with a diagnosis of aortic stenosis were alive 5 years after the diagnosis was first established and only 1 of 5 was still alive 10 years after the diagnosis.

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Long-Term Follow-Up of Isolated Replacement of the Aortic or Mitral Valve with the Starr-Edwards Prosthesis

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Review of 1,684 cases of isolated aortic or mitral valve replacement with a Starr-Edwards prosthesis demonstrated that the procedure provides improved life expectancy over that found in the natural history of valvular heart disease. Further improvement in results depends on continued reduction in operative and late mortality and in the incidence of thromboembolism. Advanced preoperative functional class, atrial or ventricular enlargement, a history of prior heart surgery, advanced age at operation and untreated valvular disease were among the factors related to increased early or late mortality. The data suggest that adequate anticoagulation, earlier performance of valve replacement and more complete repair of valvular dysfunction may increase survival rates.

The various models of the Starr-Edwards ball-valve prosthesis have had the most extensive use at the Mayo Clinic. The first mitral valve prosthesis was implanted in April 1961 and the first aortic valve prosthesis in January 1963. We have recently reviewed this experience in detail to assess late survival statistics and the incidence of complications, and to identify factors related to these events.

Isolated Aortic Valve Replacement

Prosthetic aortic valve replacement was performed in 1,555 patients at the Mayo Clinic between January 1963 and January 1972. At least one additional valve or the ascending aorta was replaced in 528 of these patients; the remaining 1,027 patients undergoing isolated replacement of the aortic valve form the basis for this review (Table I). Aortic stenosis was a more common valvular problem than was aortic insufficiency, and male patients greatly outnumbered female patients (Table II). Ninety-one percent of the patients were classified in New York Heart Association functional classes III and IV.

Surgical Results

Early mortality: There were 65 deaths within the first 30 days of valve replacement, resulting in an overall operative mortality rate of 6 percent (Table III). Dysrhythmias and myocardial failure were the leading causes of early mortality (Table IV). Preoperative functional class was the only factor found to be statistically associated with higher operative mortality rates. These rates were 4 percent for patients in functional class II, 6 percent for patients in class III and 15 percent for patients in class IV.

Late mortality: There were 259 late deaths among the 957 patients who survived operation and had complete follow-up. Sudden unexplained death and death due to coronary artery disease and

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thromboembolism were the principal categories (Table V). Data on late deaths in the survivors of operation are illustrated in actuarial fashion in Figure 1. The type of Starr-Edwards prosthesis used was not a factor in late survival (Fig. 2). Left ventricular size (Fig. 3) and type of dominant aortic valve lesion (Fig. 4) were found to be related to late survival.

Thromboembolism. In contrast to late survival, the incidence of thromboembolism was found to be related to the model of valve used (Fig. 5). The incidence of thromboembolic episodes 3 years postoperatively was 34 percent in patients with the pre-1000 series prosthesis and less than 5 percent for patients with the 1260 and 2310 series. There was no difference in incidence of thromboembolism between patients with the 1260 valve and those with the cloth-covered 2310 valve. Anticoagulation with sodium warfarin provided protection against thromboembolism. Adequate anticoagulation was defined as maintenance of the prothrombin time at a level 1.5 to 2

TABLE I

Aortic Valve Replacement with Starr-Edwards Prosthesis (1963–1972): Initial Procedure

Procedure	Patients no.	Patients %
Aortic alone	1,027	66
Aortic + mitral	320	21
Aortic + resection or repair of ascending aorta	75	5
Aortic + repair of one or more associated valves	74	5
Aortic + mitral + tricuspid	55	3
Aortic + tricuspid	4	
Total	1,555	100

TABLE II

Isolated Aortic Valve Replacement with Starr-Edwards Prosthesis (1963–1972): Sex and Age Distribution of 1,027 Patients

	Dominant Aortic Lesion			
	Stenosis	Insufficiency	Stenosis + Insufficiency	Total
Patients (no.)				
Total	507	280	240	1,027
Male	376	231	200	807
Female	131	49	40	220
Age (yr)				
Range	20–80	12–74	18–78	12–80
Average	57.0	46.1	52.6	53.0

TABLE III

Isolated Aortic Valve Replacement with Starr-Edwards Prosthesis (1963–1972): Early Deaths by Aortic Lesion

Dominant Aortic Lesion	Cases (no.)	Early Deaths no.	Early Deaths %
Stenosis	507	35	7
Insufficiency	280	21	8
Stenosis + insufficiency	240	9	4
Total	1,027	65	6

TABLE IV

Isolated Aortic Valve Replacement with Starr-Edwards Prosthesis (1963–1972): Early Mortality*

Cause	Cases no.	Cases %
Dysrhythmia	18	28
Operating room death (poor myocardial function)	10	15
Hemorrhage	9	13
Coronary disease	8	12
Low cardiac output	7	10
Thromboembolism	4	6
Infection	4	6
Valve failure	1	2
Pulmonary complication	1	2
Renal failure	1	2
Hepatic failure	1	2
Cerebrovascular accident	1	2
Total	65	100

* Within 30 days after operation.

TABLE V

Isolated Aortic Valve Replacement with Starr-Edwards Prosthesis (1963–1972): Late Deaths Among 957 Patients*

Cause	Late Deaths no.	Late Deaths %
Sudden unexpected death	64	25
Coronary artery disease	44	17
Thromboembolism	38	15
Congestive heart failure	23	9
Bacterial endocarditis	22	8
Valve failure	18	7
Thrombus	7	3
Dehiscence	7	3
Variance	4	1
Malignant disease	13	5
Dysrhythmia	6	2
Pulmonary complications	5	2
Anticoagulant complications	3	1
Miscellaneous	23	9
Total	259	100

* Alive 30 days after operation with complete follow-up, July 1972

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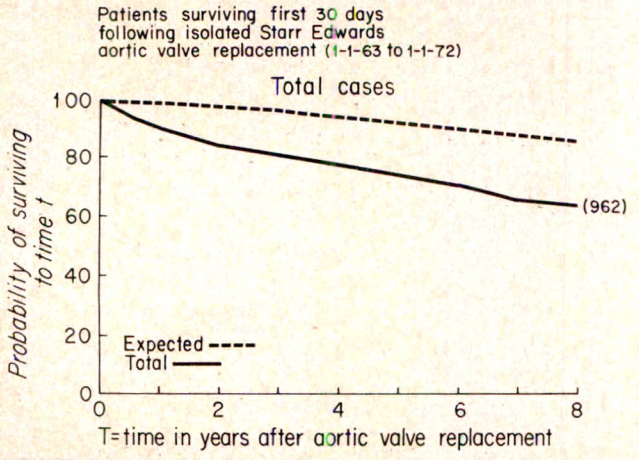

FIGURE 1. Late survival statistics in operative survivors of isolated Starr-Edwards aortic valve replacement.

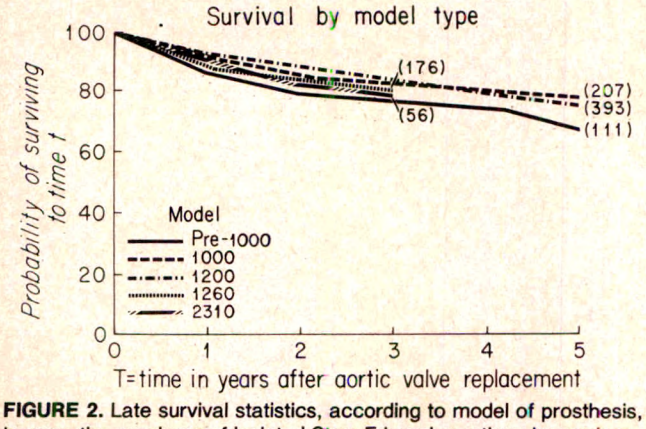

FIGURE 2. Late survival statistics, according to model of prosthesis, in operative survivors of isolated Starr-Edwards aortic valve replacement.

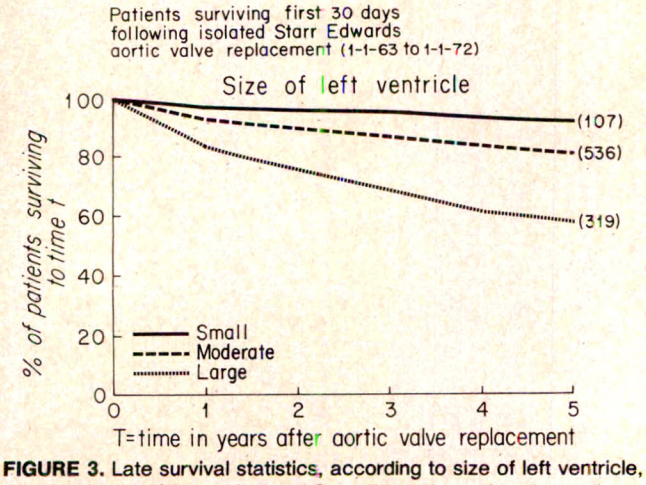

FIGURE 3. Late survival statistics, according to size of left ventricle, in operative survivors of isolated Starr-Edwards aortic valve replacement.

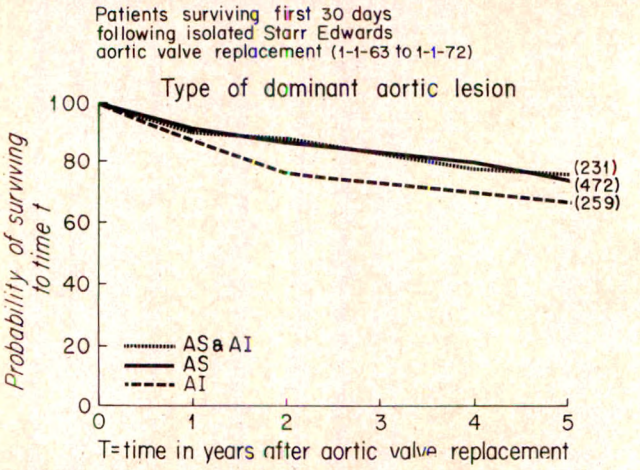

FIGURE 4. Late survival statistics, according to dominant aortic lesion, in operative survivors of Starr-Edwards aortic valve replacement.

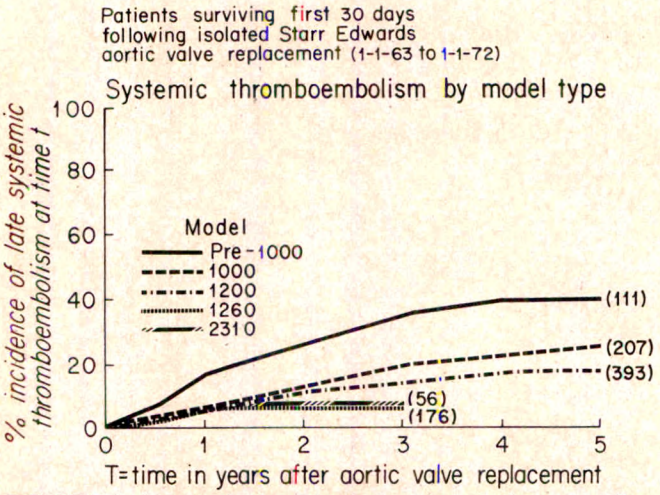

FIGURE 5. Incidence of late systemic thromboembolism, according to model of prosthesis, in operative survivors of isolated Starr-Edwards aortic valve replacement.

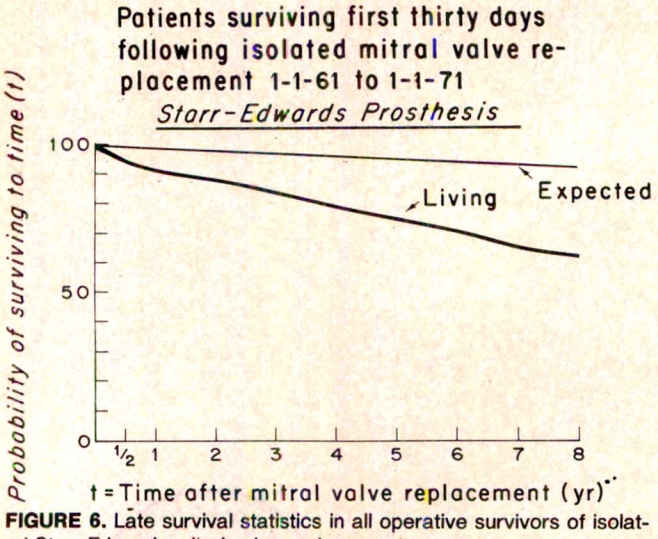

FIGURE 6. Late survival statistics in all operative survivors of isolated Starr-Edwards mitral valve replacement.

TABLE VI

Mitral Valve Replacement with Starr-Edwards Prosthesis (1961–1972): Initial Procedure

Procedure	Patients no.	Patients %
Mitral alone	657	57
Mitral + aortic	320	28
Mitral + tricuspid	58	5
Mitral + aortic + tricuspid	55	5
Mitral + tricuspid annuloplasty	56	5
Total	1,146*	100

* Excludes 63 cases, 30 in which other valve prostheses were used, 15 with complex congenital heart disease, 12 with coronary arterial surgery, and 6 for miscellaneous causes.

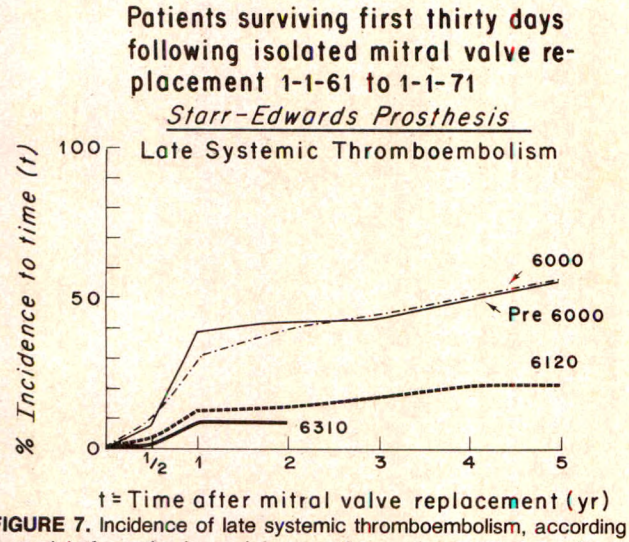

FIGURE 7. Incidence of late systemic thromboembolism, according to model of prosthesis used, in operative survivors of isolated Starr-Edwards mitral valve replacement.

times the control level on at least 75 percent of the occasions tested. The 70 percent of patients who had adequate anticoagulation by these criteria had an 11 percent 3 year incidence rate of thromboembolism. The 21 percent of patients with inadequate anticoagulation had a 25 percent 3 year incidence rate. In 9 percent of patients treatment with anticoagulant drugs was stopped or never started; these patients had a 35 percent 3 year incidence rate of thromboembolism.

Isolated Mitral Valve Replacement

The mitral valve was replaced with a Starr-Edwards prosthesis in 1,146 patients between April 1961 and January 1972 (Table VI). Data on the 657 patients with isolated replacement of the mitral valve will be reviewed. Ninety-seven percent of the patients were classified preoperatively in New York Heart Association functional classes III and IV. Male patients comprised 40 percent and female patients 60 percent of the total patient population. An almost

TABLE VII

Isolated Mitral Valve Replacement with Starr-Edwards Prosthesis (1961–1972): Clinical Features of 648 Patients* by Model Type

Patients	Model Type Pre-6000	6000	6120	6310
no.	118	127	342	61
% with prior heart surgery	38	38	32	30
% with prior CHF	55	50	55	54
% with heart disease of rheumatic origin	89	84	85	84

* Excludes 9 patients with cloth-covered valves (2 with model 6500, 3 with model 6300 and 4 with model 6320) because there were too few cases for analysis.
CHF = congestive heart failure.

TABLE VIII

Early Deaths* After Isolated Mitral Valve Replacement with Starr-Edwards Prosthesis (1961–1972)

Years	Cases (no.)	Deaths no.	Deaths %
Jan. 1961–July 1966	257	54	21
July 1966–Jan. 1972	400	39	10
Total	657	93	14

* Within 30 days after operation.

TABLE IX

Isolated Mitral Valve Replacement with Model 6120 Starr-Edwards Prosthesis (March 1966–January 1972): Size of Left Atrium and Early* Deaths

Left Atrial Size	Cases (no.)	Early Deaths no.	Early Deaths %
Small	60	1	2
Moderate	225	14	6
Large	57	16	28
Total	342	31	9

* Within 30 days of operation.

equal number of patients had stenosis, insufficiency or mixed stenosis and insufficiency as the dominant mitral valve lesion. The largest subgroup of patients had replacement of the mitral valve with the model 6120 prosthesis (Table VII).

Surgical Results

The operative mortality rate for the entire 11 year period was 14 percent with significant reduction in more recent years (Table VIII). The late mortality rate among the 562 patients surviving operation was 25 percent during the 11 year period. The 8 year actuarial survival statistics to January 1971 are shown in Figure 6. Thromboembolism was significantly related to the model of prosthesis used (Fig. 7).

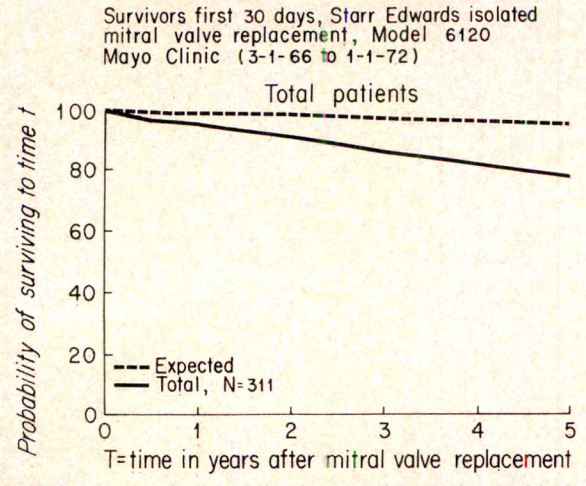

FIGURE 8. Late survival statistics in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120 (March 1966 to January 1972).

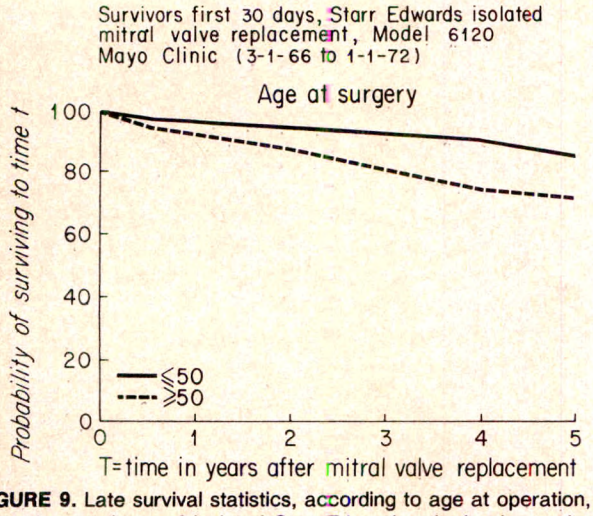

FIGURE 9. Late survival statistics, according to age at operation, in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.

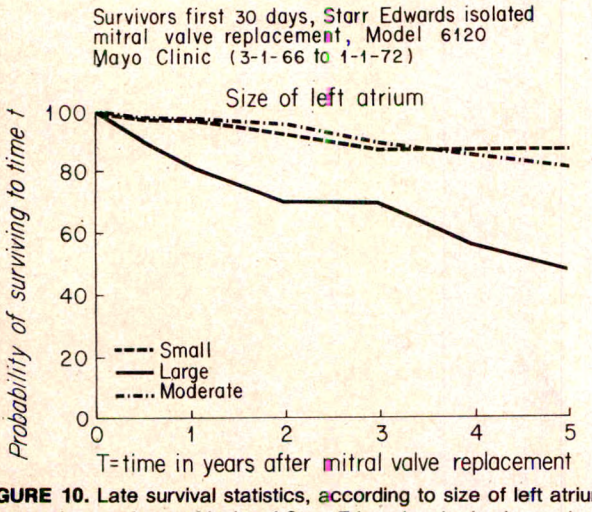

FIGURE 10. Late survival statistics, according to size of left atrium, in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.

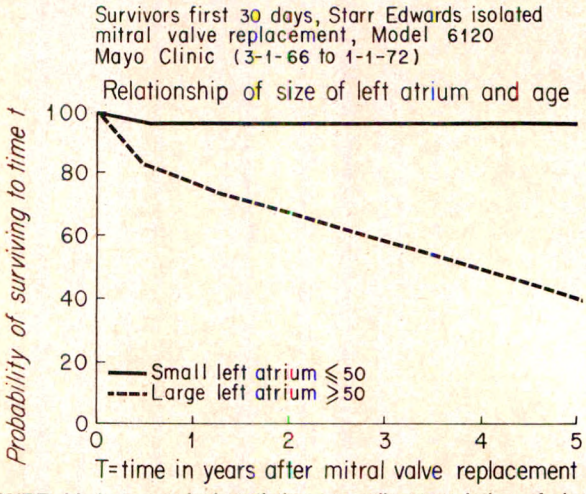

FIGURE 11. Late survival statistics according to relation of size of left atrium and age in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.

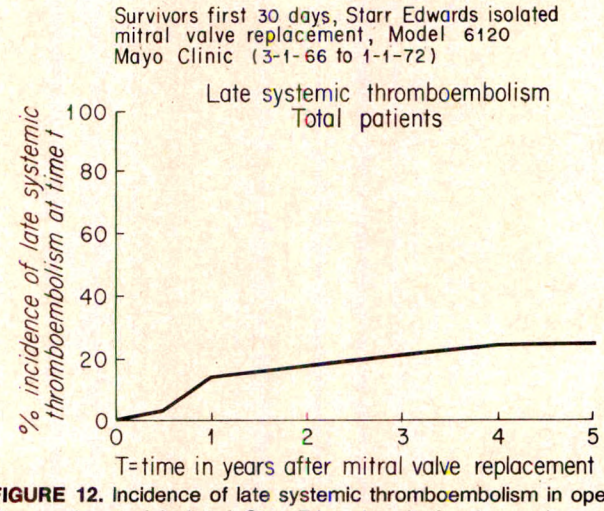

FIGURE 12. Incidence of late systemic thromboembolism in operative survivors of isolated Starr-Edwards mitral valve replacement with prosthesis model 6120.

In attempting to identify clinical features associated with early and late mortality, and with thromboembolism, we concentrated on the 342 patients who underwent replacement of the mitral valve with the 6120 prosthesis between March 1966 and January 1972.

Surgical Results (Model 6120 Prosthesis)

Early mortality: There were 31 early deaths among these 342 patients (operative mortality rate 9 percent). Low cardiac output, coronary artery disease and dysrhythmias were the leading causes. Multiple clinical and operative factors were assessed with use of discriminant analysis. Three factors were found to be associated with increased operative mortality: left atrial enlargement, advanced preoperative functional class and a history of prior heart surgery. Patients with a large left atrium had a considerably higher mortality than did patients with a small or moderate-sized left atrium (Table IX). There were no deaths among patients in functional class II, but the mortality rate was 7 percent among patients in functional

class III, and 25 percent among patients in functional class IV.

Late mortality: The 311 patients surviving operation were followed up for a mean period of 38 months. Forty-six of these patients have died (late mortality rate 15 percent). The actuarial survival curve shows progressive divergence from the general population even 5 years postoperatively (Fig. 8). Again, the assessment of multiple clinical variables indicated the relation of three factors to late mortality: patient age at operation, size of left atrium and involvement of more than one cardiac valve (Fig. 9 and 10). Patients who were less than 50 years of age at the time of operation and who had a small left atrium had a 97 percent probability of surviving 5 years, whereas patients older than 50 years with a large left atrium had only a 40 percent likelihood of surviving 5 years (Fig. 11).

Thromboembolism: The incidence rate of thromboembolism among this subgroup of patients was 25 percent 5 years postoperatively (Fig. 12), but the rate increased only minimally after the first postoperative year. The factors found to be important predictors of the occurrence of thromboembolism were the adequacy of anticoagulant therapy, the presence of left atrial thrombus at time of operation and left atrial size. Patients receiving adequate anticoagulant therapy had one third the incidence of thromboembolism manifested by patients receiving inadequate therapy. Patients with a small left atrium had a 5 percent incidence rate of thromboembolism at 5 years with no increase in rate after the second postoperative year in contrast with a 28 percent incidence rate in patients with a moderate-sized or large left atrium.

Discussion

Frustration with a relentless clinical deterioration or sudden death in patients with aortic or mitral valve disease led to the search for satisfactory valvular prostheses. Ross and Braunwald[4] pointed out the relatively short survival time of patients with aortic stenosis after the onset of symptoms. Although patients with aortic insufficiency experience a more gradual decline in clinical state, their long-term prognosis is also poor.[1,5] Olesen[3] best chronicled the natural history of mitral stenosis and noted that the median survival time of his patients treated nonoperatively was only 6 to 7 years. To be considered successful, surgical treatment of valvular heart disease must both improve the quality of life and result in a lower overall mortality rate than that found in the natural history of the disease.

Operative mortality for replacement of cardiac valves has progressively decreased with better understanding of myocardial protection and air embolism and with improved postoperative management. The early mortality rates in our series—6 percent for aortic valve replacement and 9 percent for mitral valve replacement with Starr-Edwards model 6120—have been lowered at our institution since completion of this review.

The survival rate 8 years after aortic valve replacement was 65 percent for operative survivors compared with 85 percent for the general population (Fig. 1). Although there is room for considerable improvement in this rate, it is significantly better than survival rates in the natural history studies cited earlier. An important fact is that 94 percent of operative survivors with a small left ventricle lived 5 years postoperatively compared with only 58 percent of patients with a large left ventricle (Fig. 3). These data indicate that late mortality rates are likely to be lowered if operation is performed before left ventricular enlargement becomes severe.

Data from patients undergoing mitral valve replacement indicate that both early and late mortality are likely to be reduced if operation is performed earlier in the course of the disease. A large left atrium and advanced functional class were associated with greater operative risk, and increased atrial size was related to higher late mortality rates. Disease of other cardiac valves, when not surgically treated at the time of aortic or mitral valve replacement, was also a factor in higher late mortality rates. This finding suggests that more complete repair of valvular dysfunction might lead to increased late survival. Patients surviving replacement of the mitral valve with the 6120 prosthesis had only a 78 percent probability of surviving 5 years after operation in contrast to 95 percent probability for the general population. However, even if one subtracts operative mortality data, this rate is significantly better than the 56 percent survival rate reported by Olesen[3] in a less severely ill population treated nonoperatively.

Systemic thromboembolism is the most serious complication associated with prosthetic valve replacement. Improvements in valve design have significantly reduced the incidence of this complication (Fig. 5 and 7). Refinements in cloth-covered valves may further reduce this incidence[2,6] without, it is hoped, introducing other problems. On the basis of our data, use of permanent anticoagulation for patients receiving a noncloth-covered Starr-Edwards prosthesis seems indicated.

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Influence of Surgery on the Natural History of Rheumatic Mitral and Aortic Valve Disease

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The rate of survival, the evolution of functional cardiac status and the incidence of major complications during a 5 year period were studied in 410 patients with rheumatic mitral or aortic valve disease, of whom 200 were treated medically and 210 by surgery. The 5 year survival rates in patients with various types of rheumatic mitral valve disease were similar (45 percent for those with mitral stenosis and 46 percent for those with mitral insufficiency or mixed mitral insufficiency and stenosis). The survival rate in patients with aortic valve disease was somewhat more favorable (64 percent).

Mitral valvulotomy had the most positive influence on mortality. The 85 percent 5 year survival rate of patients who underwent this procedure was significantly higher than that of patients with medically treated mitral stenosis. In patients submitted to mitral and aortic valve replacement, the survival rate was also improved in comparison with data in the corresponding medically treated groups, but to a lesser degree (70 percent for aortic valve replacement and 60 percent for mitral valve replacement). In all surgically treated groups, initial operative mortality was the primary determinant of the rate of survival at the end of 5 years.

Survivors of all surgical groups had appreciable improvement in cardiac functional classification and a remarkable reduction in the incidence of heart failure and atrial fibrillation. The incidence of infectious endocarditis was significantly reduced after mitral valvulotomy, as compared with the incidence in patients with medically treated mitral stenosis. Mitral and aortic valve replacement did not reduce the incidence of infectious endocarditis. The incidence of thromboembolic phenomena was favorably influenced by mitral valvulotomy and aortic valve replacement, but not by mitral valve replacement.

Surgical treatment of valvular heart disease by valvulotomy, valvuloplasty or prosthetic valve replacement is the only form of therapy that can relieve the mechanical overload imposed on the heart by the valvular lesion. It has the disadvantages of being expensive and practicable only in very well equipped specialized centers and of exposing the patient to a variable risk of death. As well expressed by Kirklin,[1] the value to a patient of any valvular operation (repair or replacement) is determined by the quality and duration of life it provides in comparison with the quality and duration of life determined by the natural history of the disease with the benefit of medical treatment.

In an effort to assess objectively the value of surgery in treating patients with rheumatic valve disease, we initiated a study of key factors in the natural history of chronic rheumatic cardiomyopathy: (1) mortality in a definite period, (2) cardiac functional classification, and (3) incidence of major complications that influence the first two factors. These variables were studied in 200 medically treated patients with diverse rheumatic valvular lesions and in 210 patients with the same lesions submitted to surgical correction.

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Material and Methods

Case Material

Starting in January 1964, a protocol was prepared at each visit for every patient with rheumatic heart disease attending the Services of Cardiology and of Cardiovascular Surgery of the University Hospital of Caracas. The protocol recorded in detail the presence of cardiac symptoms and the occurrence of major complicatons (heart failure, atrial fibrillation, cerebral vascular accidents, pulmonary infarction and other thromboembolic phenomena, active rheumatic fever, infectious endocarditis and complications of prostheses in those who underwent valve replacement). Each patient's functional cardiac classification, according to the criteria of the New York Heart Association, was also established at each visit. A total of 585 patients with chronic rheumatic valvular disease were followed up in this manner for 5 years.

From this group, 410 patients with either mitral or aortic valve disease were selected for study. A rheumatic origin was firmly established in all cases. Only those patients who experienced cardiac symptoms (functional classes II, III and IV) at some time during the observation period were included. Patients with multiple valvular lesions were excluded. The entire group of 410 patients was classified as follows:

Group 1 (medical treatment only): Two hundred patients received medical treatment alone for various reasons: (absence of sufficiently safe surgical means during the period of study, judgment that surgical risk was too great at that time in our hospital, incorrect medical decision, rejection of operation by the patient, and other considerations). The patients' ages ranged from 11 to 68 years (mean 35.6 years). This group contained three subgroups:

Subgroup 1A (pure mitral stenosis): There were 58 patients in this category. Their ages ranged from 11 to 68 years (mean 38 years).

Subgroup 1B (mitral insufficiency or combined mitral stenosis and insufficiency): Ninety-nine patients comprised this subgroup, 70 with mitral stenosis and insufficiency and 29 with mitral insufficiency alone. Their ages ranged from 12 to 67 years (mean 32.4 years).

Subgroup 1C (aortic valve disease): Of the 43 patients in this subgroup, 30 had mixed aortic stenosis and insufficiency, 8 had aortic stenosis alone and 5 had aortic insufficiency alone). Their ages ranged from 13 to 66 years (mean 31.4 years).

Group 2 (surgical treatment): Two hundred ten patients were treated surgically. Their ages ranged from 12 to 64 years (mean 34 years). This group contained three subgroups:

Subgroup 2A (mitral valvulotomy): The 118 patients in this subgroup ranged in age from 12 to 63 years (mean 32.5 years).

Subgroup 2B (mitral valve replacement): There were 45 patients in this subgroup. The age range was 15 to 55 years (mean 32.3 years).

Subgroup 2C (aortic valve replacement): This subgroup contained 47 patients whose ages ranged from 19 to 57 years (mean 37.3 years).

Valve Prostheses

For mitral valve replacement, Starr-Edwards prostheses, models 6310 and 6320, were used in 26 cases, Starr-Edwards model 6120 in 10 cases, Starr model 6900 in 2 cases, Kay-Shiley disk valve in 5 cases and Bjork-Shiley disk valve in 2 cases.

For aortic valve replacement, the Bjork-Shiley disk valve was used in 20 cases, Starr-Edwards model 1200 in 10 cases, Starr-Edwards model 2300 in 7 cases and Starr-Edwards models 2310 and 2320, totally covered with Teflon® and with stellite ball, in 10 cases.

Variables Studied

The rate of survival for each year was studied in all groups using the actuarial method,[2,3] which allows the expression of survival in a percentage form, in relation to the number of patients "exposed" to the possibility of living during the 5 year period of observation. The mathematical formula used to calculate the rate of survival for each year takes into account the number of deaths, the number of survivors remaining in the study and the number of patients lost to follow-up.[2]

Data on cardiac functional classification in each group or subgroup were expressed as the relation between the number of patients belonging to each class and the number of living patients being followed up at each given period of time.

The incidence of cardiac complications in each group or subgroup was expressed as the relation between the number of patients who experienced such a complication and the number of living patients being followed up during the study period.

The statistical significance of the differences found in the rate of survival for the different groups or subgroups under study was calculated by the Z test, used in large samples. The level of significance is set up to $\alpha = 5$ percent in two-tail tests. This gives $Z_{0.025} = 2.24$. To compare two differences, when needed, the test of difference of proportions was used.[4]

Results and Discussion

Rate of Survival

Medically treated group: The actuarial survival curves of 200 medically treated patients with rheumatic valve disease who were followed up for 5 years are shown in Figure 1. For the total group, the survival rate remained high (96 percent) until the 2nd year, dropping significantly to 87 percent at the end of the 3rd year. It then continued a progressive downward trend in the 4th and 5th years, reaching 52 percent at the close of the 5th year.

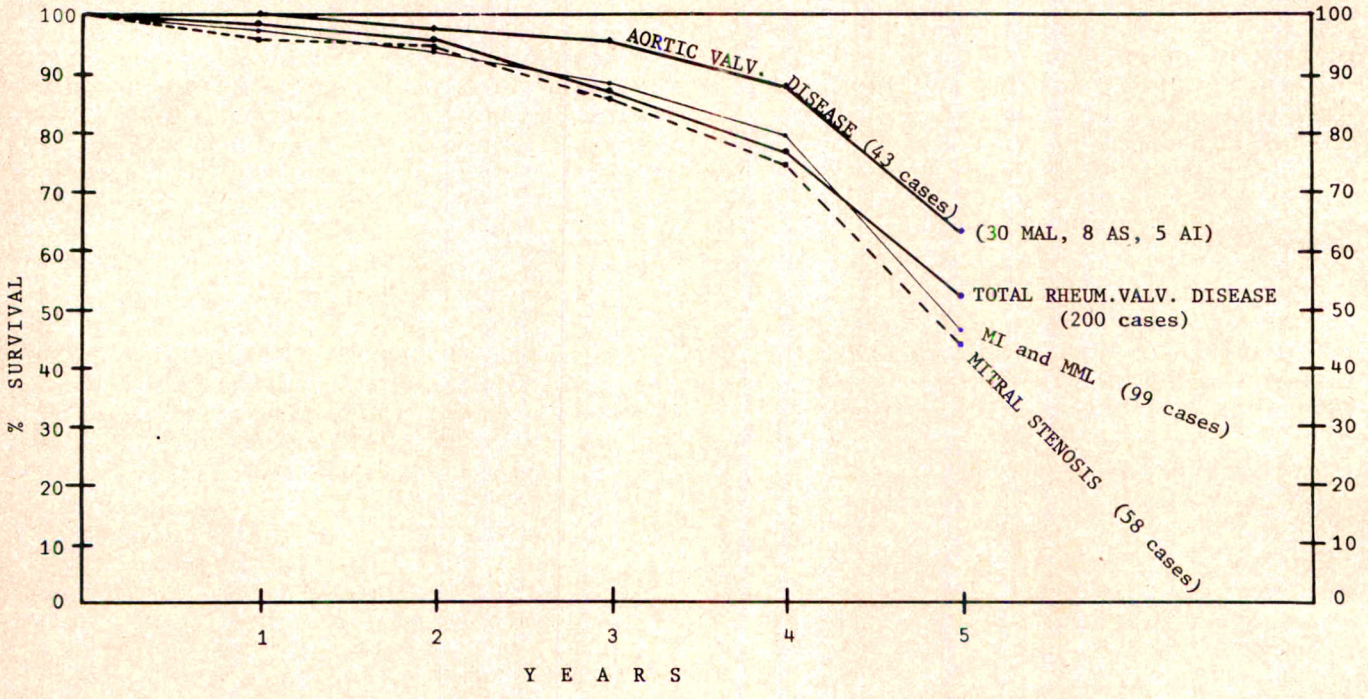
In patients with mitral stenosis survival curves were similar to those of the total group. Mortality was greater during the 4th and 5th follow-up years and the 45 percent 5 year survival rate somewhat lower than in the total group. Others[5,6] have reported a comparable evolution for pure mitral stenosis.

The patients with mitral insufficiency and combined mitral stenosis and insufficiency had a curve of survival almost identical to that of patients with pure mitral stenosis. The survival rate in this group was 46 percent at the end of the 5th year. Thus the 5 year survival rate of patients with mitral valve disease was essentially the same regardless of the type of valvular lesion.

Patients with isolated aortic valve lesions had a more favorable survival curve when compared with the entire group of patients with rheumatic valve disease or with patients with isolated mitral valve le-

sions. The rate of survival in this group was 96 percent at the end of the 3rd year, but it dropped progressively to 88 percent at the end of the 4th year and to 64 percent at the end of the 5th year.

Surgically treated group: Figure 2 shows the actuarial survival curves for the various subgroups of surgically treated patients with mitral and aortic rheumatic valve disease. It is clear that mitral valvulotomy, performed with extracorporeal circulation in nearly all cases, had the most favorable effect on survival. Operative mortality rates were very low so that the rate of survival at the end of the 1st month was



MAL = Mixed Aortic Lesion. AS = Aortic Stenosis. AI = Aortic Insufficiency.
MI = Mitral Insufficiency. MML = Mixed Mitral Lesion.

FIGURE 1. Actuarial survival curves in 200 cases of rheumatic valve disease treated medically.

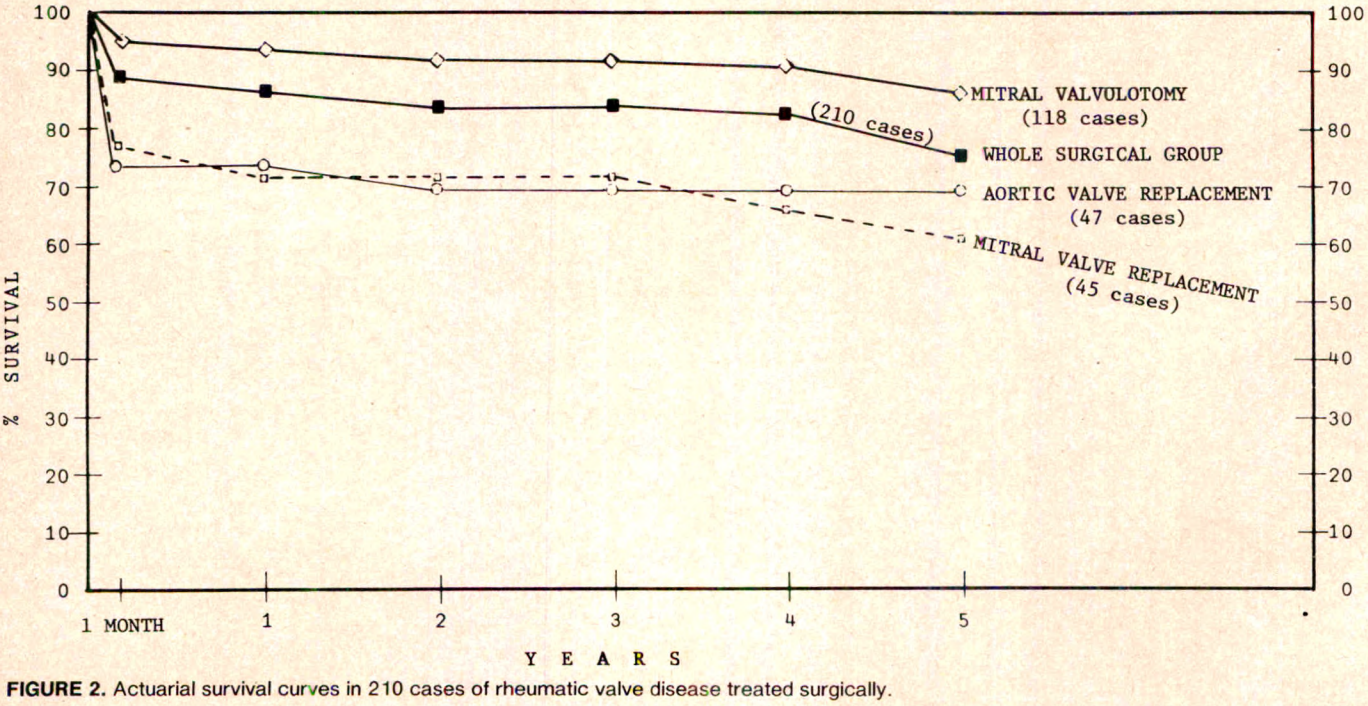


FIGURE 2. Actuarial survival curves in 210 cases of rheumatic valve disease treated surgically.

95 percent. The survival rate remained above 90 percent until the end of the 4th follow-up year. Between the 4th and the 5th years, there was an increase in mortality, with a survival rate of 85 percent at the end of the 5th year.

Patients with aortic valve replacement had a survival rate of 70 percent at the end of the 5th year. This low rate largely reflected operative mortality. The survival rate of 73 percent at the end of the 1st month was only slightly reduced by the end of the 5th year. In fact, only two late postoperative deaths were registered during the entire observation period.

Patients with mitral valve replacement had a somewhat lower (60 percent) 5 year survival rate than those with aortic valve replacement, but the difference was not statistically significant (Z_c = 0.81). As in patients with aortic valve replacement, the low 5 year survival rate was primarily determined by the operative mortality: At the end of the 1st postoperative month, the rate of survival was 76 percent. At the close of the 1st year it dropped to 71 percent, and this level was maintained during the next 3 years. After the 4th year it dropped to 67 percent and, at the end of 5 years, to 60 percent.

We conclude that the most favorable influence on the 5 year survival rate is exerted by mitral valvulotomy and that the lower 5 year survival rate in patients with aortic and mitral valve replacement is determined by the operative mortality. As operative mortality continues to decrease, the rate of long-term survival will also increase.

Comparison of medically and surgically treated groups: *Mitral valvulotomy:* Figure 3 compares the 5 year survival curve of patients with rheumatic mitral stenosis treated medically with that of patients submitted to mitral valvulotomy. The beneficial effect of the operation on the survival curve is evident. Operative mortality rates were low, so that the rate of survival at the end of the 1st month was 95 percent. In succeeding years, the survival rate was unchanged; it dropped to 91 percent at the end of the 4th year and to 85 percent at the end of the 5th year. This 5 year survival rate is significantly higher than the 45 percent rate in patients with mitral stenosis treated medically (Z_c = 5.37).

Mitral valve replacement: Mitral valve replacement is indicated in patients with mitral insufficiency, mixed mitral lesions or calcified mitral stenosis or extreme deformity of the valve. The survival curve of patients undergoing this operation was therefore compared with the curves of the two groups of patients whose mitral valve disease was treated only medically: those with mitral insufficiency or mixed mitral lesions and those with mitral stenosis alone (Fig. 4). The two medically treated groups had identical, rapidly descending survival curves and, together, had a 45 percent 5 year survival rate.

By contrast, the group undergoing mitral valve replacement had, without deduction of operative mortality, a survival rate of 60 percent toward the end of the 5th postoperative year, a rate higher than that of the two groups treated medically. It is clear that the lower 5 year survival rate, by comparison with patients undergoing valvulotomy, was fundamentally due to operative mortality.

Aortic valve replacement: Patients undergoing aortic valve replacement had a 70 percent 5 year rate of survival (Fig. 5). This rate was 10 percent higher than the rate for patients undergoing mitral valve replacement but only 6 percent higher than that of patients whose aortic lesion was treated medically. These differences in survival rates are related to the

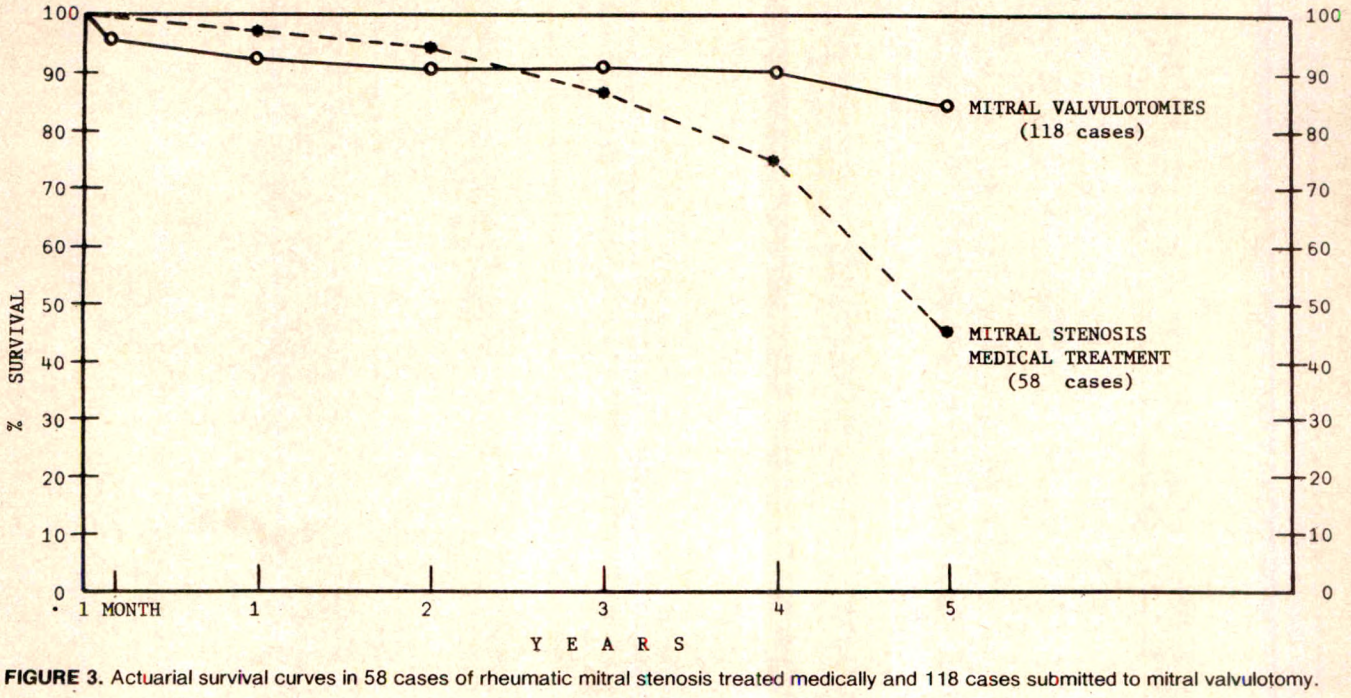


FIGURE 3. Actuarial survival curves in 58 cases of rheumatic mitral stenosis treated medically and 118 cases submitted to mitral valvulotomy.

higher survival rates for medically treated aortic valve disease (64 percent) by comparison with medically treated mitral valve disease (45 percent).

The statistical method of differences of proportions[4] was used to compare the effects of mitral and aortic valve replacement on survival rates in relation to survival rates in the corresponding valvular disease treated medically. The following results were obtained: For every 100 patients with mitral valve disease, 15 more would be alive at the end of 5 years if submitted to mitral valve replacement than if medically treated. For every 100 patients with aortic valve

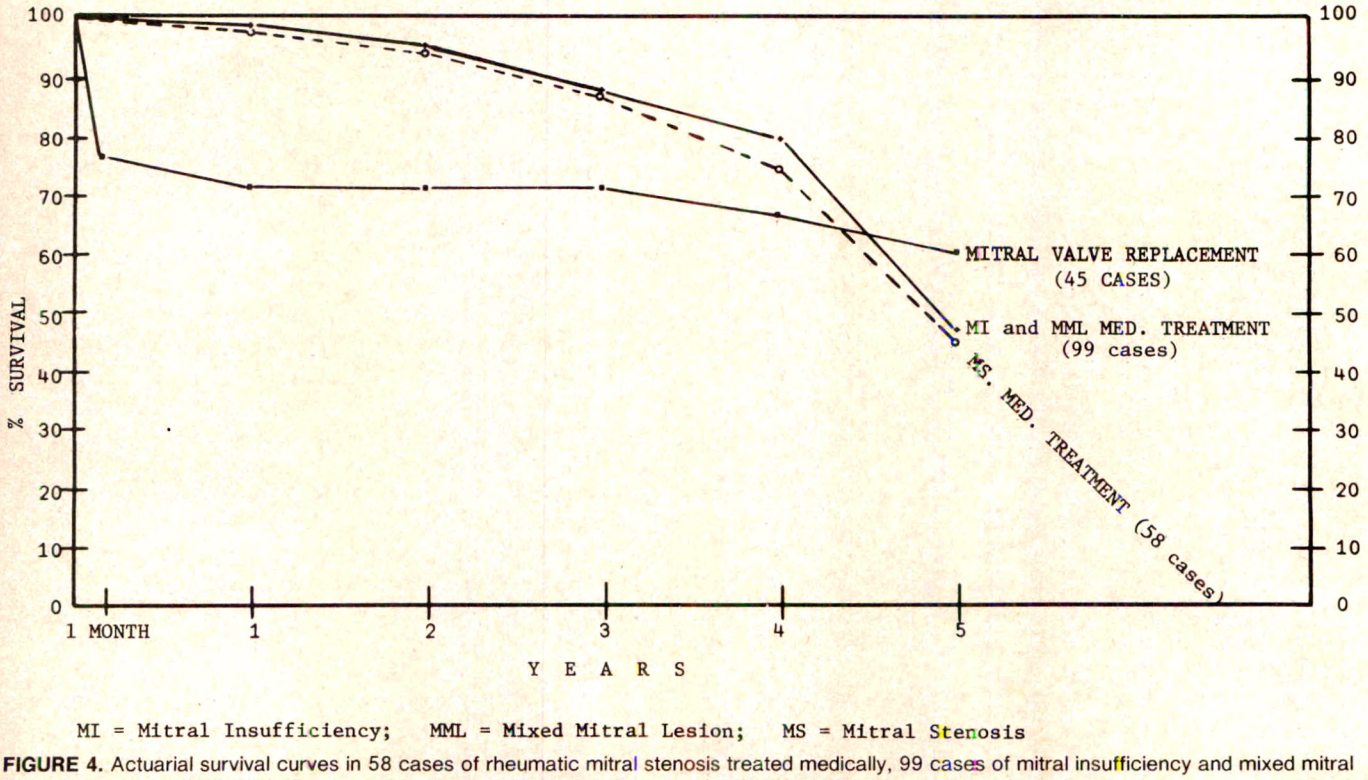


FIGURE 4. Actuarial survival curves in 58 cases of rheumatic mitral stenosis treated medically, 99 cases of mitral insufficiency and mixed mitral lesions treated medically and 45 cases of rheumatic mitral valve disease submitted to mitral valve replacement.

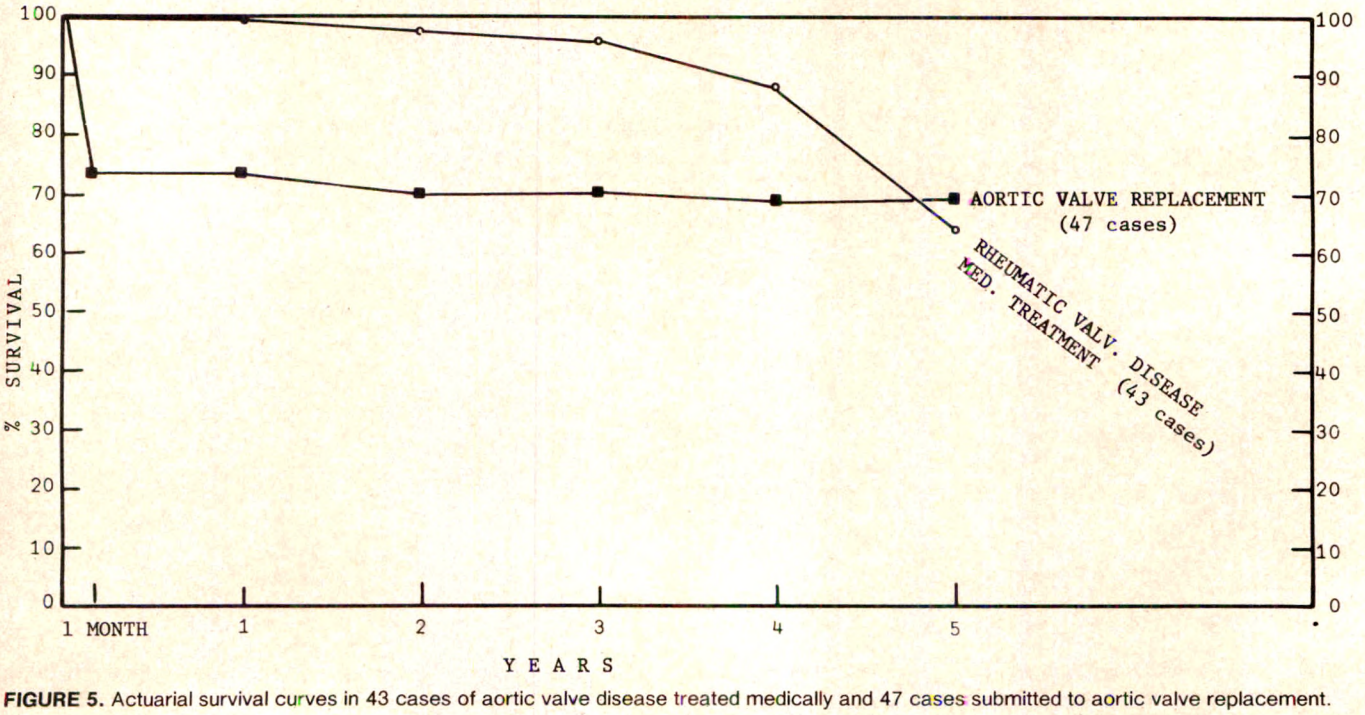


FIGURE 5. Actuarial survival curves in 43 cases of aortic valve disease treated medically and 47 cases submitted to aortic valve replacement.

disease, 7 more would be alive at the end of 5 years if submitted to aortic valve replacement than if medically treated.

Evolution of Functional Classification

Mitral valve disease: Figure 6 shows the evolution of functional classification in patients with mitral valve disease treated medically, and by mitral valvulotomy and valve replacement. Percentages were established in relation to the total number of surviving patients who were followed up every year.

In patients with medically treated mitral stenosis, mitral insufficiency and mixed mitral lesions, the evolution of functional classification was similar. In the 1st year, the majority (60 percent) had class II status, a minor percentage were in classes I and III and an insignificant percentage in class IV. In subsequent years, a progressive decrease in patients in classes I and II is clearly noticed as is the progressive increase of patients in classes III and IV. At the close of the 5th year, a little more than 40 percent were in class IV, more than 75 percent belonged to classes III and IV and there were no patients in class I. Progressive functional deterioration of mitral valve disease is thus evident, regardless of the type of lesion.

For the group subjected to mitral valvulotomy, during the preoperative period there were no patients in class I; 50 percent were in class III, 33 percent in class II and 17 percent in class IV. During the 1st postoperative year, the patients' functional classification decidedly improved: 46 percent were in class I, 30 percent in class II, 18 percent in class III and only 6 percent in class IV. In subsequent years, a similar proportion was maintained—with predominance of class I over class II, class II over class III and, finally, class III over class IV. However, there was a slight progressive decrease in patients in classes I and II with a corresponding increase in patients in classes III and IV.

The patients who required mitral valve replacement had more severe functional deterioration preoperatively than did patients who underwent valvulotomy: 62 percent were in class III and 25 percent in class IV. In the 1st year after operation, nearly 90 percent were in classes I and II and only a small percentage were in classes III and IV. This favorable distribution held throughout the 5 year study period, with a slight increase in patients in classes III and IV and a corresponding decrease of patients in classes I and II. By the end of the 5th year, 83 percent were still in classes I and II.

If we compare mitral valvulotomy with mitral valve replacement, we observe that at the end of the 5th year, the functional class is lower in patients with valve replacement. The explanation for this difference is that clinical deterioration of patients after valvulotomy is due to various factors, such as insufficient valvulotomy, iatrogenic mitral insufficiency and

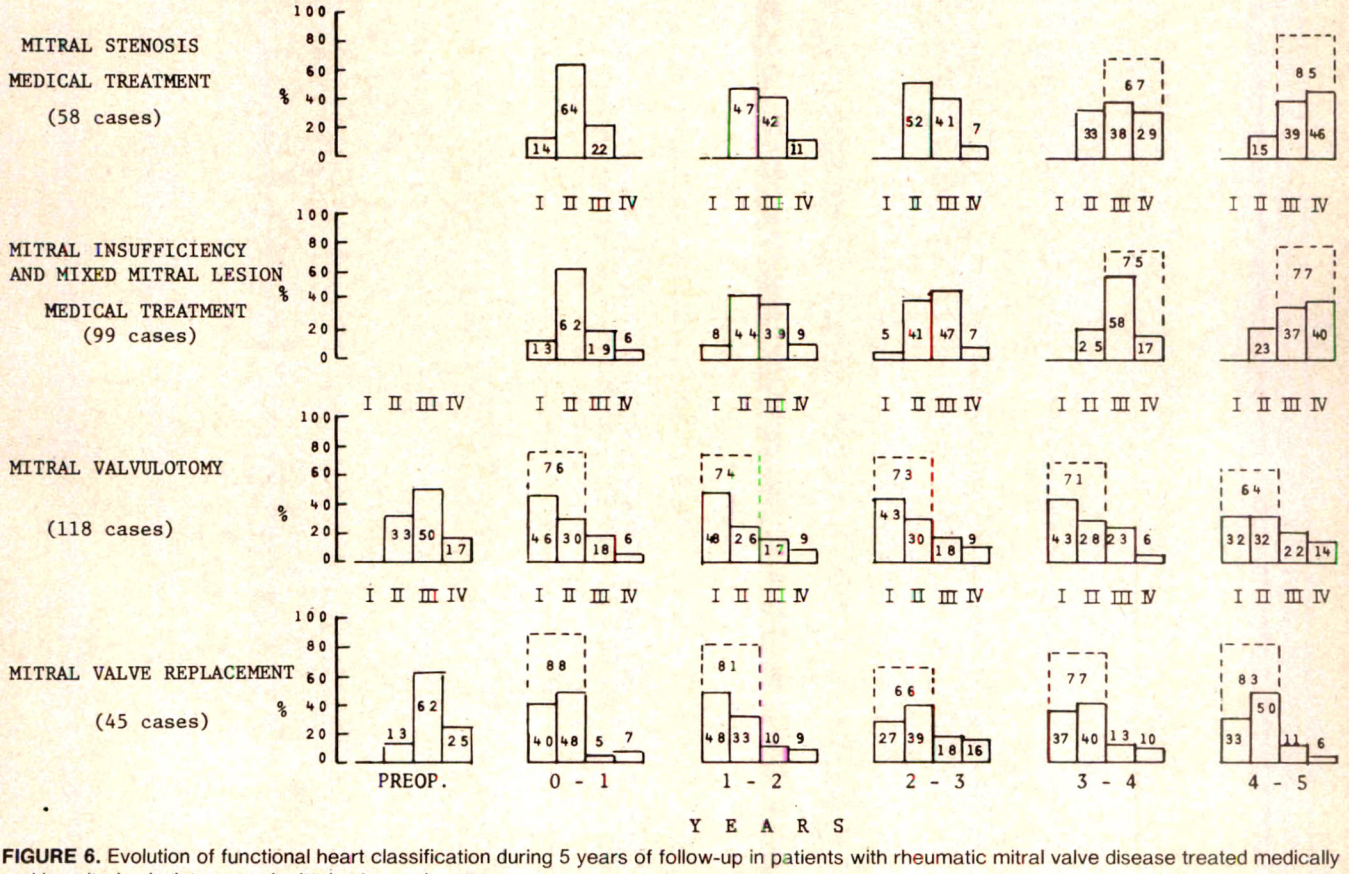


FIGURE 6. Evolution of functional heart classification during 5 years of follow-up in patients with rheumatic mitral valve disease treated medically and by mitral valvulotomy and mitral valve replacement.

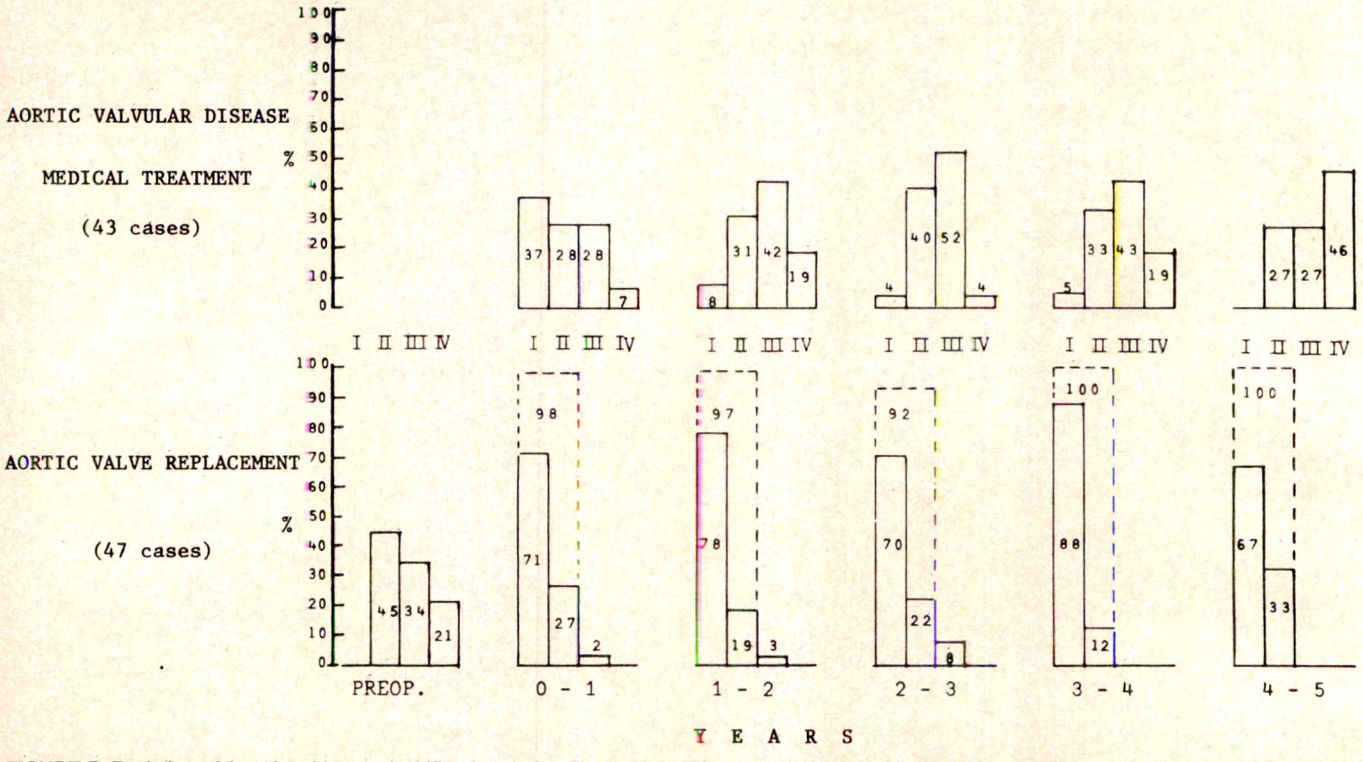


FIGURE 7. Evolution of functional heart classification during 5 years of follow-up in patients with rheumatic aortic valve disease treated medically and by aortic valve replacement.

TABLE I

Complications During 5 Years of Follow-Up in Patients with Mitral Valve Disease Treated Medically and by Mitral Valvulotomy and Mitral Valve Replacement*

Group Studied	Heart Failure	Atrial Fibrillation	Thromboembolism: Cerebrovascular Accident	Thromboembolism: Pulmonary Infarction	Thromboembolism: Other	Thromboembolism: Total	Active Rheumatic Fever	Infectious Endocarditis	Complications of Prosthesis
Medical treatment									
Mitral stenosis (58 patients)									
no.	41	28	11	12	1 (multiple)	24	4	2	
%	70.6	48.2	19	20.6	1.7	41.3	6.8	3.4	
Mitral insufficiency and mixed mitral lesions (99 patients)									
no.	72	40	8	6	1 (renal)	15	8	2	
%	72.7	40.4	8.1	6.1	1.1	15.2	8.1	2	
Surgical treatment									
Mitral valvulotomy (118 patients)									
no.	23	19	2	5	...	7	2	2	
%	19.4	16.1	1.7	4.2		6	1.7	1.7	
Mitral valve replacement (45 patients)									
no.	10	11	5	3	...	8	1	3	6 (partial detachments)†
%	22.2	24.4	11.1	6.6		17.7	2.2	6.6	13.3

* After the 1st postoperative month in patients treated surgically.
† 3 with significant mitral regurgitation and 3 with discrete mitral regurgitation.

a tendency to restenosis. In patients with mitral valve replacement, deterioration is caused only by structural and hemodynamic imperfections of the prosthesis, factors that act in a slower evolutionary manner. In both groups a certain degree of evolutionary deterioration is inevitable because neither surgical procedure reverses myocardial dysfunction, which is present in various degrees, even in cases of pure mitral stenosis.[7–10]

Aortic valve disease: Figure 7 shows the evolution of functional classification in patients with aortic valve disease treated medically and by aortic valve replacement. In the medically treated group, patients who remained asymptomatic during the 5 year follow-up period were excluded. All patients who were included manifested symptoms (dyspnea, angina or syncope) at some time during the period of observation. During the 1st year, an insignificant percentage of patients were in class IV; the majority were distributed uniformly among classes I, II and III, with a slightly greater percentage (37 percent) in class I (asymptomatic). From the 2nd year on, the number of patients in class I decreased progressively until there were no patients in this group; the number of patients in classes III and IV increased progressively and in class II decreased moderately, so that by the end of the 5th year patients in class IV predominated (46 percent), the percentage of patients in classes II and III was similar (27 percent) and there were no patients in class I. Thus, progressive functional deterioration is also evident in patients with aortic valve disease treated only medically.

The patients undergoing aortic valve replacement had the following preoperative status: 45 percent in class II, 34 percent in class III and 21 percent in class IV. Survivors of the operation, during the 1st year were classified as follows: class I 71 percent, class II 27 percent, class III 2 percent, and class IV none. Throughout the 5 year postoperative period, about 100 percent were in classes I and II, with a progressive decrease in asymptomatic patients in class I and a proportionate increase in patients in class II. It is evident that aortic valve replacement improves the functional capacity of patients with rheumatic aortic valve disease and notably slows the progressive functional deterioration characteristic of these patients.

Incidence of Complications

Mitral valve disease: Table I shows the incidence of the most frequent major complications in mitral valve disease treated medically and surgically by valvulotomy or valve replacement. Heart failure and atrial fibrillation had a definitely lesser incidence in both surgical groups than in the medical group.

The incidence of thromboembolic phenomena for the medically treated group was 41 percent in patients with mitral stenosis and 15 percent in those with mitral insufficiency or mixed mitral lesions. In the surgical group, the incidence was 6 percent for mitral valvulotomy and 18 percent for mitral valve replacement. This greater incidence of thromboembolic phenomena after mitral valve replacement is determined by the structural characteristics of the prosthetic valves that make them thrombogenic. Changes in prosthetic valves are being introduced so as to reduce this effect particularly in models totally covered with Teflon or similar material.[1,11–14]

Infectious endocarditis was observed in 3.4 percent of patients with mitral stenosis and 2 percent of those with mitral insufficiency and mixed mitral lesions medically treated. The incidence was 1.7 and 6.6 percent, respectively, for patients treated by mitral valvulotomy and mitral valve replacement. The incidence of infectious endocarditis was thus three times greater in valve replacement than in mitral valvulotomy.

Partial detachment of the prosthetic valve occurred in six cases (13.3 percent), with severe mitral regurgitation in three and mild mitral regurgitation in three.

Aortic valve disease: Table II shows the incidence of complications in patients with aortic valve

TABLE II

Complications During 5 Years of Follow-Up in Patients with Rheumatic Aortic Valve Disease Treated Medically and by Aortic Valve Replacement*

Group Studied	Heart Failure	Atrial Fibrillation	Thromboembolism: Cerebrovascular Accident	Thromboembolism: Pulmonary Infarction	Thromboembolism: Other	Thromboembolism: Total	Active Rheumatic Fever	Infectious Endocarditis	Complications of Prosthesis
Medical treatment (43 patients)									
no.	31	4	2	9		11	2	1	
%	72	9.3	4.6	21		25.5	4.6	2.3	
Valve replacement (49 patients)									
no.	4		2			2		1	2 (partial detachments)
%	8.8		4.2			4.2		2.1	4.2

* After the 1st postoperative month in patients treated surgically.

disease treated medically and by aortic valve replacement. Again, the incidence of heart failure and atrial fibrillation was remarkably less after aortic valve replacement than in aortic valve disease treated medically.

Thromboembolic phenomena appeared in 25 percent of patients treated medically—almost all (21 percent) represented by pulmonary infarction—and in 4.2 percent of those with valve replacement.

Infectious endocarditis had equal incidence, a little more than 2 percent, in both groups. In two patients (4.2 percent) partial detachment of the aortic prosthesis occurred.

The following conclusions can be drawn from these observations on the incidence of complications: The incidence of heart failure and atrial fibrillation was remarkably reduced by all three surgical operations (mitral valvulotomy, mitral valve replacement and aortic valve replacement). The incidence of infectious endocarditis was significantly less after mitral valvulotomy than in medically treated mitral stenosis. Mitral and aortic valve replacement did not reduce the incidence of infectious endocarditis in our series. This finding reflects a limitation of replacement procedures, since prostheses, being foreign material, favor infection. The incidence of thromboembolic phenomena was favorably influenced by mitral valvulotomy and aortic valve replacement, but not by mitral valve replacement.

Our findings regarding the incidence of thromboembolic phenomena after valve replacement are not conclusive since different types of prostheses were used for both mitral and aortic valve replacement. The architectural structure of the prosthesis significantly influences the incidence of thromboembolic episodes and a major reduction of such complications has been observed in a series of patients who received prostheses with improved antithrombogenic structure.[1,11,13,14] Detachment and mechanical complications of prostheses continue to be a limitation of the benefits obtained from valve replacement.

Acknowledgment

The surgical team that performed the operations was headed by Dr. Rubén Jaén, Chief of the Service of Cardiovascular Surgery of the University Hospital of Caracas. We acknowledge the assistance of Lic. Freddy Zambrano, School of Statistics of the Universidad Central of Venezuela, in the statistical analysis of the data.

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Effects of Alcohol on Cardiovascular Performance After Experimental Nonpenetrating Chest Trauma

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Electrocardiographic and hemodynamic correlates were recorded before and after a standardized nonpenetrating blow to the chest in 9 anesthetized control dogs (Group I), 5 dogs pretreated with alcohol, 0.4 g/kg intravenously (Group II), and 12 dogs undergoing chest trauma after alcohol infusions (Group III). In animals in Group I, transient major arrhythmias, including complete heart block and ventricular tachycardia, occurred immediately after impact. One animal died with ventricular fibrillation. In the eight survivors these disturbances were accompanied by acute reductions in aortic pressure and cardiac index; values for both variables gradually increased after restoration of sinus mechanism. Alcohol alone (Group II) produced no significant alterations in either hemodynamic performance or electrical activity, but when combined with nonpenetrating chest injury (Group III) it caused a mortality rate of 92 percent, the majority of animals dying with electromechanical dissociation. Mean survival time in Group III was 23.1 ± 6.5 (standard error of the mean) minutes compared with 80.3 ± 9.6 minutes in Group I. At autopsy, minor cardiac lesions of either the pericardium or myocardium were observed in all animals in Groups I and III, but none were considered lethal. It is concluded that administration of alcohol, even in small doses, can effect catastrophic reductions in mechanical performance in the presence of otherwise nonfatal cardiac injury secondary to nonpenetrating chest trauma. The clinical implications of this association are discussed.

Previous studies from this laboratory[1,2] have demonstrated in a canine model system that nonpenetrating chest trauma causes major changes in left ventricular performance. Traffic accident statistics indicate that such trauma can occur in man, usually after violent contact with the steering column and other fixed automobile accessories in a high speed collision. Such injuries represent a leading cause of death, particularly in younger age groups.[3,4] Data from several agencies[5] have strongly incriminated excess alcohol intake as a precipitating factor in such fatalities, and alcohol has been shown to have direct pharmacologic effects on the heart, including both stimulation[6–10] and depression[11–20] of mechanical performance, inducement of electrical pacemaker asystole and cardiac arrest,[2,7,9] and a depression in peripheral vasomotor tone, resulting in increased susceptibility to trauma and shock.[12,18] To date, the specific effects of alcohol on the cardiovascular system after nonpenetrating chest trauma have not been defined. In this study we evaluated and compared several indexes of cardiac performance in response to chest trauma and alcohol, considered both selectively and in combination, in the canine model system previously described.

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Methods

Twenty-six mongrel dogs, weighing 8.4 to 26.0 kg (average 16.3), were anesthetized with intravenously administered pentobarbital (15 mg/kg body weight) and, after cuffed endotracheal intubation, maintained with methoxyflurane and oxygen under conditions of controlled ventilation. Determinations of arterial pH, and partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2) and carbon dioxide combining power were obtained throughout the studies to assure adequacy of ventilation and acid-base balance.

Animals were secured firmly in the supine position as described previously.[1,2] Polyethylene catheters (inner diameter 0.125 inch) were placed in the superior vena cava or right atrium by way of the right jugular vein, and into the aorta by cannulation of a femoral artery. Each catheter was connected to a P23DB Statham pressure transducer for monitoring venous and arterial pressures. Cardiac output determinations were performed by the indicator-dilution method by injecting indocyanine green dye into the superior vena cava or right atrium and sampling from the distal aorta. A pneumotachometer was placed about the animal's lower chest to monitor respirations. All signals, including a monitoring electrocardiographic lead, were amplified and displayed on a·DR12 Electronics for Medicine recorder.

The trauma delivery system consisted of two components[1]*:* The first element, a cast aluminum disk, 6.5 cm in diameter and 1.5 cm thick, covered with a thin protective layer of rubber, was centered over the lower sternum of the animal at approximately the fifth intercostal space and secured by adhesive straps. The second element, a Cash-X captive bolt pistol device (supplied by Accles and Shelvoke, Ltd., Talford St. Works, Birmingham, England), was centered perpendicularly at the disk midpoint and fired at end-expiration. The pistol was fixed to a restraining platform to provide even distribution of pressures at the point of impact, to dissipate recoil forces uniformly and to permit remote firing. Bench studies using this system discharged into clay were conducted with a monitoring strain gauge attached to a hollow cylinder interposed between the pistol bolt and the aluminum disk. Impact profiles were developed and demonstrated a spike force of 248 kg occurring maximally at 1 msec and returning to 0 kg by 7 msec. Reproducibility between trials was ±0.5 percent. With careful attention to directing the blow to a site on the midsternal axis opposite to the fifth intercostal spaces, a selective injury to the heart was produced with little additional trauma to other organ systems. Injuries to the latter included slight contusions of small segments of overlying lung and occasional rib fractures.

Protocol: All experiments were conducted according to the Guide for Laboratory Animal Facilities and Care as outlined by the Institute of Laboratory Animal Resources, National Academy of Sciences. Electrocardiographic and hemodynamic data including values for central venous pressure, systemic arterial pressure, cardiac index (defined as cardiac output normalized for animal weight) and peripheral vascular resistance (calculated as the ratio of systemic arterial pressure to cardiac index) were obtained during a resting period in all animals. The protocol was divided into three sections. In the first series of experiments, in nine animals (average weight 13 kg) (Group I), a single standardized blunt chest blow was delivered to the midsternum after control observations. Hemodynamic and electrocardiographic determinations were repeated 0, 10, 30, 60 and 90 minutes after impact and compared with pretrauma values. At the conclusion of the 90 minute trial period, all animals were killed and detailed postmortem examinations of the heart made to determine the extent and location of any gross pathologic injuries to the pericardium or myocardium resulting from the closed chest impact.

In two separate experiments, 5 animals in Group II (average weight 15 kg) and 12 in Group III (average weight 17 kg) were pretreated with intravenous infusions of alcohol (0.4 g 200 proof ethanol/kg). Venous blood for assay of alcohol levels was sampled 10 minutes after completion of the infusions. Hemodynamic and electrocardiographic data were obtained at intervals similar to those described for Group I after a 10 minute stabilization period following the infusion of alcohol. No other intervention was introduced to dogs in Group II, but dogs in Group III received a blunt chest blow identical to that administered to animals in Group I. In Group III, either at the end of the 90 minute trial period in surviving animals or after experimental death, postmortem examination of the heart was performed to quantitate the degree of gross anatomic injury.

Statistical analysis: Intragroup statistical comparisons of hemodynamic performance were made between pre- and post-impact data in all groups using the paired Student *t* test; intergroup comparisons of Groups I and III and Groups II and III were performed using the nonpaired Student *t* test. Statistical significance was defined for probability values of less than 5 percent. Among the electrocardiographic changes observed after trauma were several disorders of rhythm and conduction, including ventricular tachycardia, ventricular fibrillation and complete heart block, either with or without independent ventricular activity. Complete heart block was identified by a total failure of antegrade atrioventricular conduction and consisted of arrhythmias either with atrial activity exclusively and no ventricular complexes (ventricular arrest) or independent atrial and ventricular complexes, the latter at less than 60 beats/min and of wide QRS configuration.[21]

Results

Group I (Impact Alone)

Hemodynamic data: Eight of nine animals survived closed chest trauma and were studied over the 90 minute observation period (mean survival time 80.3 ± 9.6 minutes). One animal died with ventricular fibrillation soon after impact (3.5 minutes). Hemodynamic responses are shown in Figure 1. Cardiac index and mean aortic pressure 10 and 30 minutes after trauma were significantly reduced from pretrauma control values ($P < 0.05$ for both variables at each time period). Thereafter, cardiac index rose gradually, whereas mean aortic pressure remained depressed for the duration of the study ($P < 0.05$). Central venous pressure as well as peripheral vascular resistance decreased gradually throughout the study, but neither was significantly lower than pretrauma control levels.

Electrocardiographic abnormalities: These were observed in all animals. In addition to morphologic changes noted in the QRS-T wave configurations, the major abnormalities included the development of disorders in rhythm and conduction. With the exception of ectopic ventricular contractions, which occurred throughout the study in all animals, these disturbances were confined to the 10 minute period immediately after impact (Fig. 2). In two animals, a brief period of ventricular tachycardia (average 13 seconds) was followed by resumption of sinus

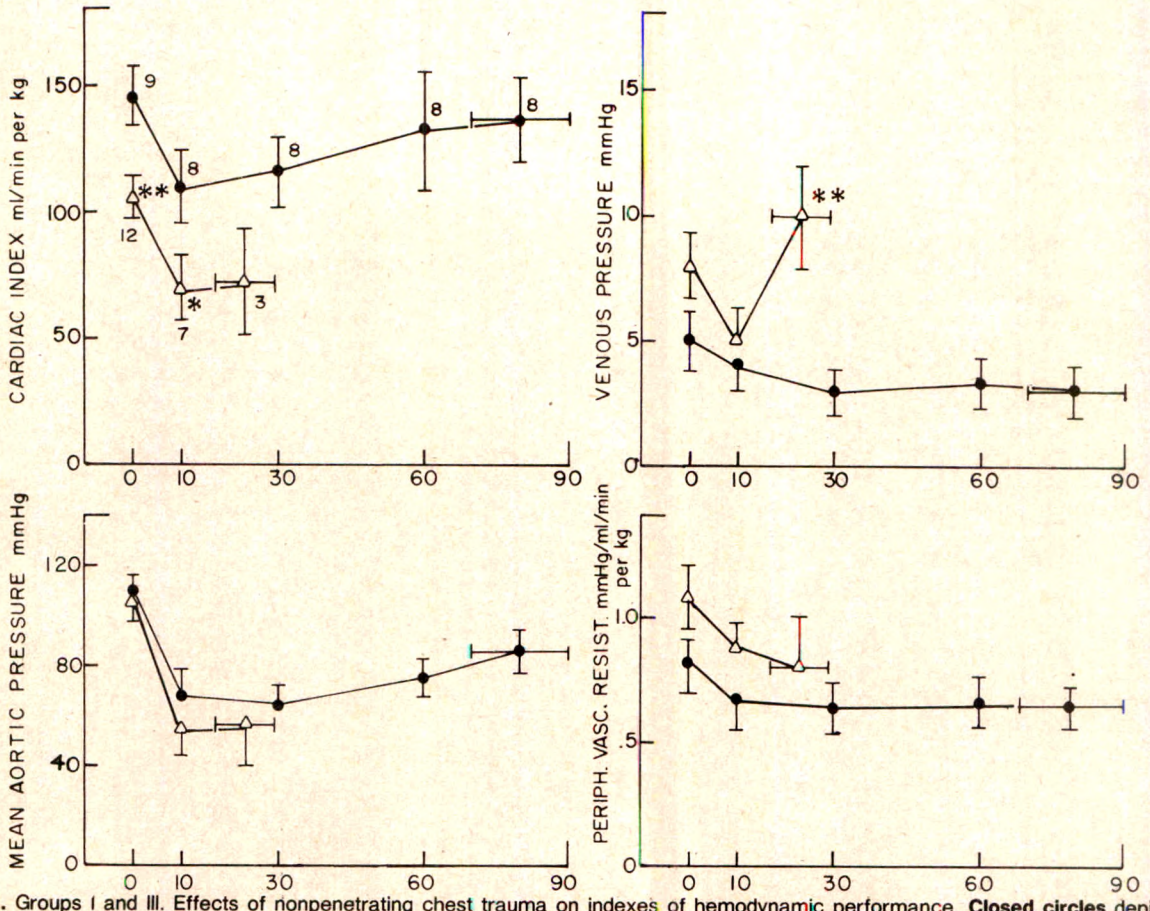

FIGURE 1. Groups I and III. Effects of nonpenetrating chest trauma on indexes of hemodynamic performance. **Closed circles** depict the responses in animals in Group I when chest trauma was evaluated selectively; **open triangles** depict responses in dogs in Group III that underwent chest trauma after pretreatment with alcohol. Bars define standard error of the mean; asterisks indicate statistical significance between groups (* = $P < 0.05$; ** = $P < 0.01$); arabic numbers in upper left panel refer to number of animals at each time period; PERIPH. VASC. RESIST. = peripheral vascular resistance.

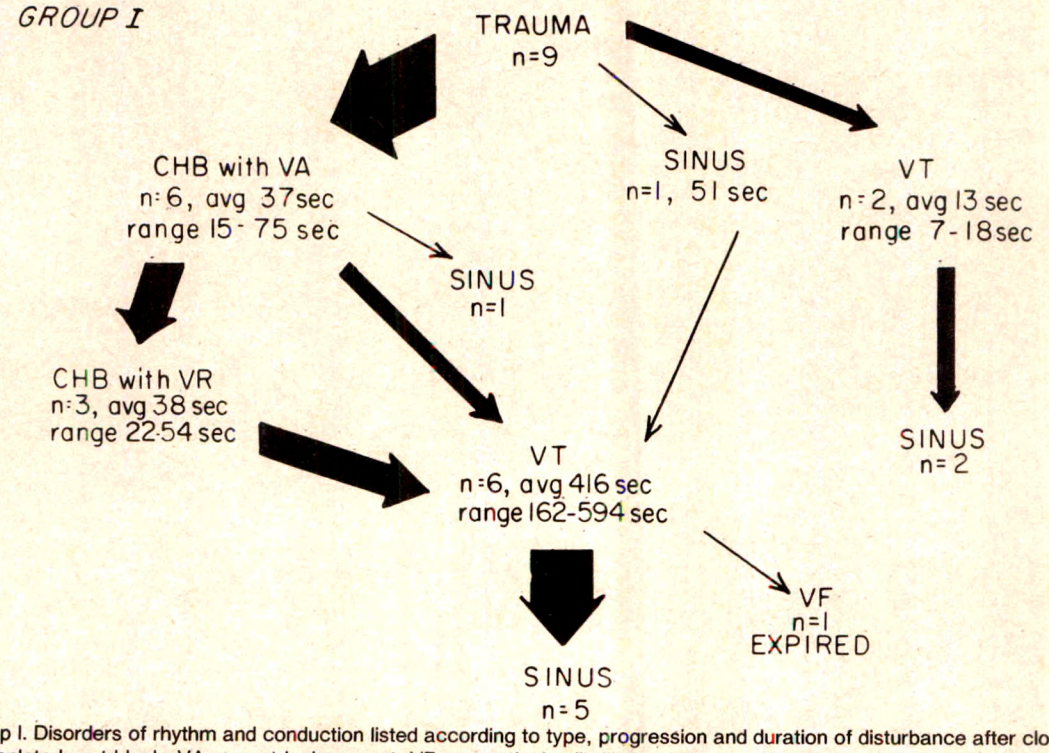

FIGURE 2. Group I. Disorders of rhythm and conduction listed according to type, progression and duration of disturbance after closed chest trauma. CHB = complete heart block; VA = ventricular arrest; VF = ventricular fibrillation; VR = ventricular response; VT = ventricular tachycardia. (Published by permission of the *American Journal of Physiology.*[2])

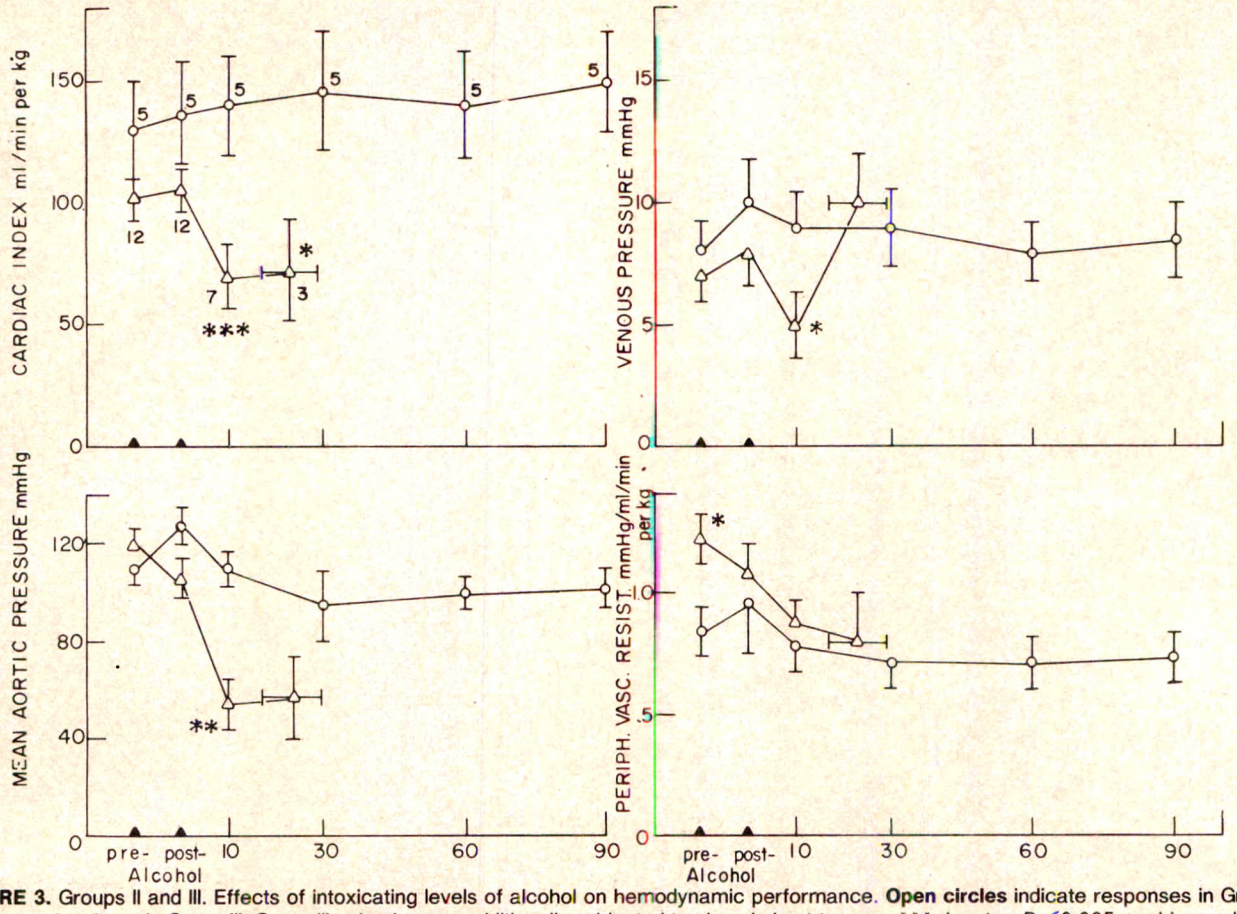

FIGURE 3. Groups II and III. Effects of intoxicating levels of alcohol on hemodynamic performance. **Open circles** indicate responses in Group II, **open triangles** those in Group III. Group III animals were additionally subjected to closed chest trauma. *** denotes $P < 0.005$; arabic numbers in upper left panel refer to number of animals at each time period.

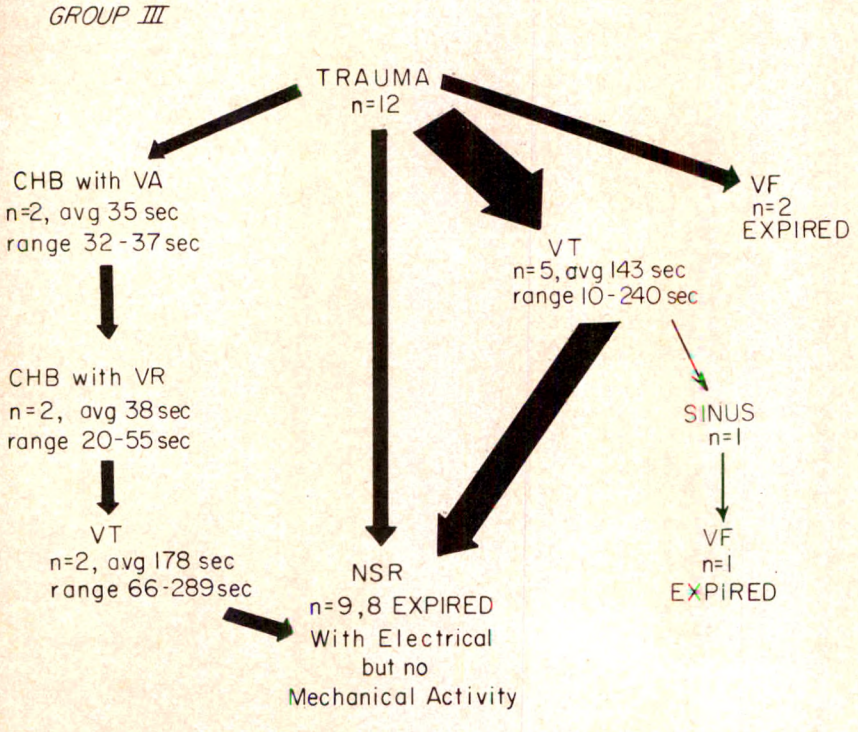

FIGURE 4. Group III. Disorders of rhythm and conduction after chest trauma. NSR = normal sinus rhythm; other abbreviations as in Figure 2. See text for discussion.

rhythm. In six of the remaining seven dogs, protracted ventricular tachycardia occurred (average duration 6 minutes, 56 seconds). In five of these six animals, ventricular tachycardia was preceded by a period of complete heart block initially with ventricular arrest (average 37 seconds) followed by the development of a slow idioventricular rhythm (average 38 seconds) in three. Of the six animals with protracted ventricular tachycardia, five manifested reversion to sinus rhythm and one died with ventricular fibrillation. Heart rate in the eight animals with reversion to sinus rhythm averaged 121.2 beats/min for the remainder of the studies; this rate was not significantly different from the rate before trauma.

Postmortem examination: Lesions in Group I were classified as either pericardial or myocardial injuries and encompassed pericardial tears, myocardial contusions or lacerations. There were no transmural or septal myocardial ruptures, valve perforations, chordae tendineae separations, coronary arterial hemorrhages, lacerations, thromboses or hemopericardium. However, 6 instances of pericardial tear, 18 instances of myocardial contusion and 3 instances of superficial myocardial laceration were observed in the nine dogs.

Group II (Alcohol Alone)

The hemodynamic values for cardiac index, mean aortic pressure, central venous pressure and peripheral vascular resistance in the five animals receiving alcohol, 0.4 g/kg intravenously, are shown in Figure 3. Blood levels of alcohol in this group averaged 132 ± 22 mg/100 ml. Administration of alcohol alone did not alter hemodynamic performance. Minor fluctuations in several of the mechanical indexes occurred over the course of the study, but none were statistically different from pretreatment values. All animals maintained sinus rhythm throughout the trial period without a significant change in heart rate (mean value 133.7 beats/min).

Group III (Alcohol Plus Impact)

Hemodynamic data: Figures 1 and 3 illustrate the hemodynamic responses to closed chest trauma after administration of alcohol (blood levels 126 ± 23 mg/100 ml) in animals in Group III. Two dogs died immediately after impact and another at 5 minutes with ventricular fibrillation; two others died at 4 and 7 minutes, respectively, with sinus rhythm but without mechanical function. In the seven animals surviving 10 minutes after impact, both cardiac index and mean aortic pressure were significantly lower than before trauma ($P < 0.025$ and $P < 0.05$, respectively). Central venous pressure and peripheral vascular resistance were also reduced, but the changes did not meet criteria for statistical difference.

Only one animal survived for the entire 90 minute observation period. Four deaths occurred between the 10 and 30 minute trial periods. Hemodynamic data for the three animals surviving past the 10 minute trial period are grouped in Figures 1 and 3 and expressed as the terminal point for Group III responses (mean survival time 23.1 ± 6.5 minutes). Cardiac index, mean aortic pressure and peripheral vascular resistance were essentially unchanged from the 10 minute responses, whereas central venous pressure was increased.

Figures 1 and 3 also compare the hemodynamic data of animals in Group III with those of animals in Groups I and II. With the exception of cardiac index, the values for Groups III and I at zero time were comparable. Responses 10 minutes after impact were again similar in both groups, although cardiac index in Group III was lower than in Group I ($P < 0.05$). The final responses in the two groups (at 23.1 minutes for Group III versus 30 minutes for Group I) were also similar, with the exception of venous pressure, which increased significantly in the three animals of Group III.

Comparisons between the two animal groups treated with alcohol (Groups II and III, Fig. 3) revealed that the additional intervention of trauma significantly increased mortality. In the seven animals in Group III surviving 10 minutes after impact, cardiac index, mean aortic pressure and central venous pressure were significantly reduced as compared with the responses for the alcohol-pretreated group not subjected to trauma. Data at 23.1 minutes for animals in Group III, as compared with either the 10 or 30 minute responses in Group II, revealed a continued depression in cardiac index and aortic pressure, whereas central venous pressure and peripheral vascular resistance were similar in both groups.

Electrocardiographic abnormalities: Major disorders in rhythm and conduction were also observed in animals in Group III in the first 10 minutes after impact (Fig. 4). Examples of transient complete heart block and protracted ventricular tachycardia were noted, as in Group I. Three animals died with ventricular fibrillation either immediately or soon after impact. The remaining nine animals all had ultimate reversion to sinus rhythm. Of these, eight died with electromechanical dissociation, that is, the continued presence of electrical activity (of sinus mechanism) without a mechanical response sufficient to support life. One such progression is shown in Figure 5.

Postmortem examination: As in Group I, there were no instances of transmural or septal myocardial ruptures, valvular perforations or avulsions, chordae tendineae tears, coronary arterial damage or hemopericardium. A comparable number of 7 pericardial tears and 20 myocardial contusions, particularly of the right ventricle, was observed in hearts in Group III. These lesions were unassociated with superficial lacerations.

Discussion

The studies have described the acute changes in mechanical performance and electrical activity that

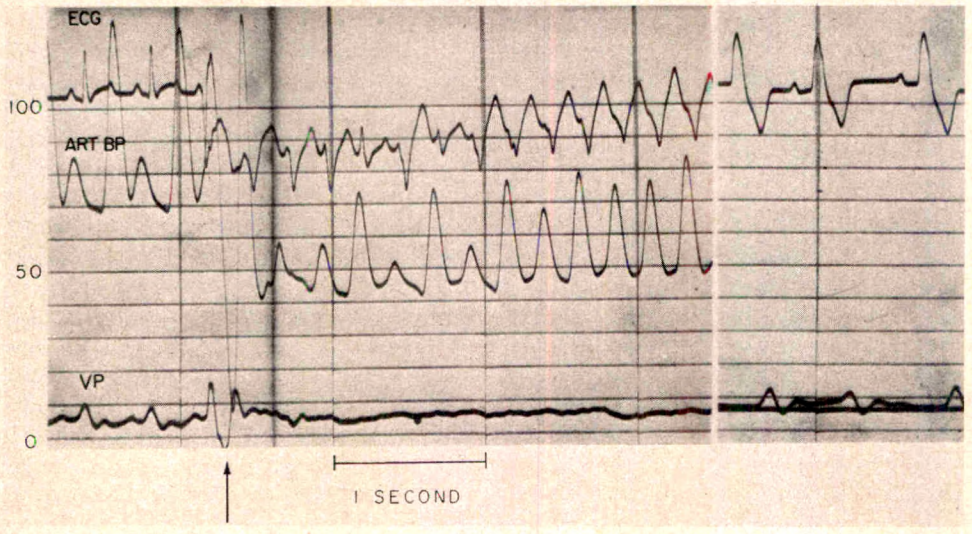

FIGURE 5. Dog from Group III. Hemodynamic and electrocardiographic data in an animal pretreated with mildly intoxicating doses of alcohol and subjected to closed chest trauma. Left panel illustrates the changes immediately after trauma **(arrow)** during which a transient bout of ventricular tachycardia was recorded. Right panel shows the phenomenon of electromechanical dissociation 7 minutes after impact. The electrocardiogram (ECG) recorded sinus mechanism with an intraventricular conduction delay while both arterial (ART BP) and venous (VP) pressures were less than 10 mm Hg.

occurred with nonpenetrating chest trauma and the administration of alcohol. Considered separately, impact injuries to the chest selectively caused several cardiac lesions, principally myocardial contusions, that resulted in early and often severe arrhythmias, disturbances in electrical conduction, and impaired hemodynamic performance. Nevertheless, eight of nine animals survived the acute injury and experienced gradual return of function. Alcohol, by itself, administered in small doses, caused no appreciable changes in either mechanical function or electrical activity. In contrast, when the two interventions were applied conjointly, a highly lethal combination was effected resulting in a mortality rate of 92 percent, the majority of animals dying with electromechanical dissociation.

Previous studies from this laboratory[1,2] have described the major arrhythmias that can occur with cardiac injury arising from blunt chest trauma and have supported previous findings in other animal models[22–24] and in man.[22,25] Possible mechanisms for their development were myocardial stretching induced by intrathoracic compressions of the heart causing the activation of ectopic pacemaker foci,[26,27] the establishment of repetitive reentry patterns secondary to electrical gradients at boundaries between normal and contused myocardium,[28,29] or localized hypoxia of specialized conducting tissue. The possibility of a neurogenic reflex mechanism was also investigated, but pretreatment with both sympatholytic or parasympatholytic agents failed to protect against the occurrence or reduce the duration of these disturbances. On postmortem examination of the hearts, the membranous portions of the interventricular septa were uninvolved, and there were no visible lesions to explain the high incidence of complete atrioventricular heart block.

Alcohol and the heart: Several conflicting reports exist concerning the role of alcohol in the heart. In various animal and clinical studies, alcohol has been alleged to have stimulating,[6–10] depressant[11–20] or no effects[17,30–33] on the heart. The reasons for this variability, as proposed by Ahmed et al.,[19] may be related to the dose of alcohol administered, the mode and duration of its administration, the type of hemodynamic variables measured, the time of measurement in relation to the peak action of alcohol, prior use of alcohol and the hemodynamic state of the subject or animal before treatment. In this study, alcohol was infused in amounts sufficient to achieve blood alcohol levels equivalent to those observed in average-sized human subjects ingesting 120 to 150 ml of 90 proof whiskey. This amount is considered small, but one in common social usage and enough to produce mild intoxication.[34]

Even when alcohol is administered in small doses, there is no consensus regarding its effects on the heart. In animal studies, several investigations[7,9,10] found an increase in cardiac output and aortic pressure with variable changes in myocardial contractility and peripheral vascular resistance. Juchems and Klobe[8] demonstrated in patients improved myocardial function at blood alcohol levels of 39 to 120 mg/100 ml. Conversely, Regan et al.[15] in anesthetized dogs found myocardial depression at blood levels of 110 mg/100 ml as did Conway[16] in patients with coronary artery disease. Riff et al.[32] found no change in myocardial performance in normal human volunteers with blood alcohol levels ranging from 85 to 136 mg/100 ml, nor did Blomqvist et al.[33] in alcohol-pretreated human volunteers undergoing graded exercise. Our data in animals in Group II support these latter observations. However, all of these results are subject to the limitations inherent in measurements by conventional techniques pointed out by Horwitz and Atkins.[20] Their investigations were able to demonstrate minor increases in left ventricular end-diastolic pressure and slight decreases in stroke volume and left ventricular maximal rate of rise of pressure using more sophisticated methods, including high fidelity, solid state pressure transducers, flowmeters and piezoelectric sonocardiometric transducers. Although

such devices were not applicable to our protocol, their data, like ours, suggest no major changes in hemodynamic function with small doses of alcohol.

Electromechanical dissociation after trauma and alcohol: Although the several hemodynamic and electrical changes observed with trauma can primarily be referred to injuries of the heart, these events must be viewed in the context of the entire cardiovascular system. In animals in Group I, trauma precipitated acute reductions in both cardiac index and systemic arterial pressure that might be expected to evoke compensatory peripheral mechanisms. These reductions were not reflected by increases in peripheral vascular resistance or central venous pressure and thus suggested a possible interference with autonomic reflexes. The addition of alcohol in this setting produced greater reductions in cardiac index and arterial pressure that implied an even further loss of peripheral compensatory mechanisms and that may have contributed mechanically to the decreased survival in dogs in Group III.

Electromechanical dissociation, the mode of death in the majority of this latter alcohol-pretreated group, is a poorly understood phenomenon used to describe a completely ineffective mechanical contraction in the presence of adequate pacemaker and conduction capabilities.[35] Seen clinically in the setting of cardiac arrest in patients with advanced coronary artery disease having extensive myocardial damage, it represents "profound cardiovascular collapse"[36] in which the most aggressive resuscitation efforts have been universally unrewarding. The mechanism for its development after the combined interventions of nonpenetrating chest trauma and alcohol is unclear. Although Steinhaus[35] has implicated the effects of depressant drugs, such as anesthetic agents, the contribution of barbiturates and methoxyflurane as primary determinants in animals in Group III seems unlikely, since these drugs were without appreciable effect in either Groups I or II. Another explanation for this finding might include the end results of prolonged systemic hypotension with coronary arterial underperfusion leading to cardiac anoxia. Its appeal is lessened somewhat by the observation that control animals subjected to impact (Group I) were able to recover although they experienced systemic hypotension for longer periods than those experienced by the alcohol pretreated dogs manifesting electromechanical dissociation. Only a small amount of myocardial tissue was contused or lacerated, or both, in hearts in Groups I and III, and there were no significant differences in the extent of injuries between groups. Perhaps the site of action of alcohol in the injured myocardium occurred at a cellular level through derangement of a primary biochemical process.

Clinical implications: It is widely appreciated that alcohol is a leading risk factor in automotive accidents; our study demonstrates that, in addition, its role in relation to specific cardiac injuries is profound, in terms of both potentiating life-threatening arrhythmias and cardiovascular collapse. This effect emphasizes the potential dangers of alcoholic excess on electrical and mechanical functions of the heart and may have a clinical analog in the sudden death of intoxicated drivers soon after seemingly minor cardiac injuries such as a small bruise of the right ventricle unassociated with other organ injury or blood loss. A clinical investigation of this relation would be of merit. It seems axiomatic that any underlying or coexisting heart disease in this setting would add yet another determinant that could only lead to a more unfavorable outcome.

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Effects of Myocardial Hypoxia and Ischemia on Myocardial Scintigraphy

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The effect of regional myocardial ischemia and hypoxia on myocardial scintigraphy was studied in patients and dogs after intravenous administration of cesium-129. Seven men with angiographically proved ischemic heart disease underwent exercise testing and ^{129}Cs was given immediately when ischemia was manifested in the electrocardiogram. Defects were not evident in the scintigrams of any patient. Failure to visualize a defect might be related to delayed uptake of ^{129}Cs by the myocardium (maximal uptake in 45 minutes). The ischemic state was dissipated before the disparity in uptake between normal and ischemic myocardium could be visualized. Cesium-129 is useful for identifying acute myocardial infarcts but should not be used to visualize transient exercise-induced regional ischemia.

Six dogs were given ^{129}Cs after induction of regional myocardial hypoxia by perfusion of the anterior descending coronary artery with venous blood. In each, scintigraphy revealed a defect that resolved after reperfusion with arterial blood. Two other dogs were given ^{129}Cs before perfusion with hypoxemic blood; neither dog manifested a defect. Since perfusion was maintained by a pump these results suggest that the major cause of the scintigraphically observed defect was inadequate cellular uptake of ^{129}Cs rather than excessive cellular loss. Since regional myocardial hypoxia produced a reversible defect, scintigraphic studies might overestimate the size of an acute myocardial infarct in man by including the ischemic zone surrounding the infarct.

Myocardial scintigraphy performed with intravenously administered radionuclides can be used to detect areas of myocardial infarction or ischemia.[1–4] The cyclotron-produced radionuclides potassium-43 and cesium-129 that have recently become available have more suitable gamma energies for deep tissue imaging than did earlier radionuclides. We have reported the effectiveness of ^{129}Cs myocardial scintigraphy in the diagnosis of myocardial infarction.[3] Since the patient's prognosis and likelihood of experiencing cardiogenic shock after myocardial infarction are related to the amount of myocardium that is infarcted, noninvasive techniques that will accurately quantify the size of an acute myocardial infarct are needed.[5,6] Quantification is also needed to evaluate the efficacy of drugs and solutions in limiting the size of a myocardial infarct[7] and to determine the possible effect of a periinfarction zone of ischemia upon the size of the defect observed in scintigrams after acute myocardial infarction. If ischemia contributes significantly to the observed defect, the size of a myocardial infarct could be overestimated by scintigraphy.

Studies designed to elucidate the possible causes of the defect seen on myocardial scintigrams obtained with ^{129}Cs have not been reported. Zaret et al.[2] using ^{43}K myocardial scans attributed the defects observed to inadequate perfusion and to ischemia-induced efflux of potassium from the myocardium.

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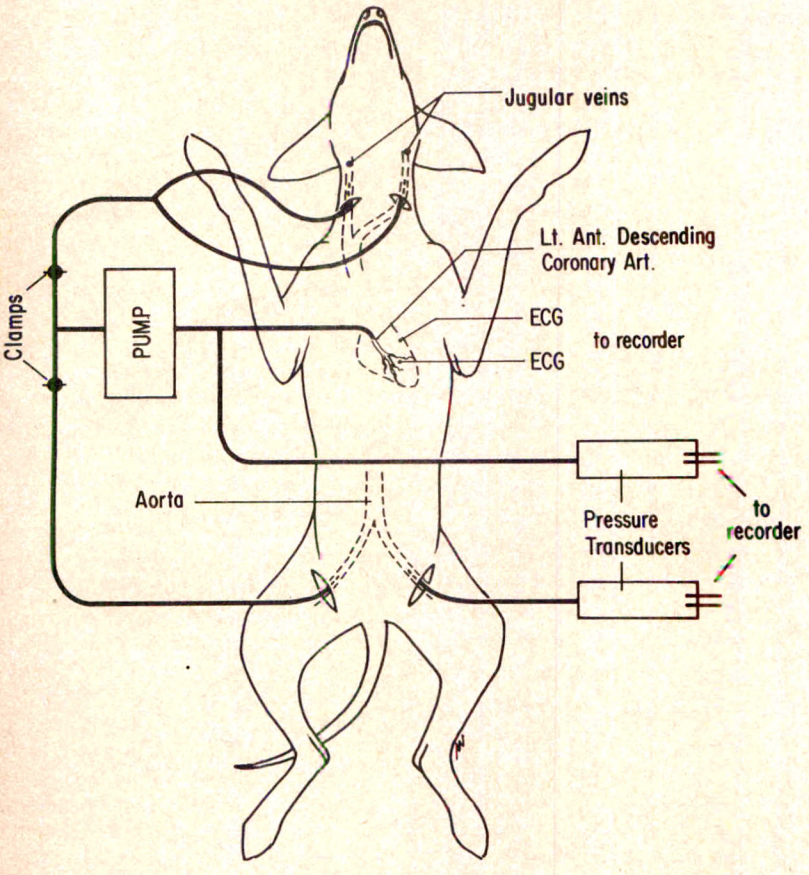


FIGURE 1. Schematic diagram of the preparation used to produce regional myocardial hypoxemia in dogs. Ant. = anterior; Art. = artery; Lt. = left.

The purpose of this study was two-fold. In patients, we studied the efficacy of intravenously administered ^{129}Cs as an agent for evaluating the effects of exercise-induced regional myocardial ischemia. In dogs, we attempted to clarify in part the several mechanisms by which ischemia may produce a defect on scintigrams obtained with ^{129}Cs. Studies in dogs were designed to separate the effects of regional hypoxemia on cellular uptake of ^{129}Cs from the more generalized effects of the regional ischemia observed in man. In ischemia, unlike hypoxemia, there is decreased coronary blood flow and perfusion pressure, decreased delivery of substrate and decreased removal of acid metabolites, all of which could contribute to a scintigraphic defect. Ischemia and hypoxemia have in common decreased oxygen tension (PO_2). It was our intent to study only the effects of regional hypoxemia. Coronary perfusion with hypoxemic blood was preserved by controlling coronary blood flow and maintaining perfusion pressure with a roller pump. If we had produced ischemia by partial occlusion of the coronary artery, we would not have been able to separate the effects of decreased delivery of radionuclide to the myocardium and increased transit time across the membrane from the effects of hypoxia. In addition, with decreased perfusion pressure the dilution of ischemic blood by collateral blood flow and preferential shunting of oxygen and radionuclide from normally perfused surrounding myocardium could have confused interpretation of the scintigrams.

Methods

Cesium-129 was produced at the Cyclotron Branch of the Naval Research Laboratory in Washington, D. C. The ^{129}Cs was extracted by the method of Sodd et al.[8] of our nuclear medicine laboratory, resulting in carrier-free ^{129}Cs. Scintigraphy was performed with a gamma scintillation camera and a coarse pinhole collimator with an energy setting of 360 kilo electron volts and a 35 percent window. Five to 10 minutes was required to obtain each view, and 200,000 counts were collected per view.

Seven men aged 38 to 57 years with known ischemic heart disease were studied. The diagnosis of ischemic heart disease was established in each patient by a history of angina pectoris, an ischemic response to a submaximal graded treadmill exercise test and coronary angiographic evidence of at least 50 percent obstruction in one or more of the major coronary arteries. One patient had clinical and electrocardiographic evidence of a prior myocardial infarction. A graded submaximal treadmill exercise test with continuous monitoring of the electrocardiogram was performed according to the protocol of Roitman et al.[9] Patients performed exercise until the appearance of angina pectoris and/or 1 mm of horizontal S-T segment depression of 0.08 second's duration in the monitored electrocardiogram. At this point, 4 mc of ^{129}Cs was administered intravenously through a scalp-vein needle that had previously been placed in the antecubital vein. Exercise was then terminated. The patient was transported immediately by a physi-

cian to the gamma camera with an accompanying portable electrocardiographic monitor and defibrillator. Scintigraphy was performed 10 minutes after administration of ^{129}Cs. Five views were obtained in the following order: left lateral, left anterior oblique, anterior, left posterior oblique and right anterior oblique.

Experimental studies: Using dogs, we designed a preparation to assess the effect of reduced oxygen delivery from obstructive coronary arterial lesions on ^{129}Cs myocardial scintigrams. To ensure adequate delivery of isotope to the myocardium, flow in the anterior descending coronary artery was controlled and hypoxemia was produced by perfusion with venous blood having a low oxygen content. In eight mongrel dogs control scintigrams were obtained 1 week before the study. Anesthesia was induced with intravenously administered pentobarbital and the dogs were artifically ventilated with a Harvard respirator. The heart was exposed through a left lateral thoracotomy. Two epicardial electrodes were sewn on the anterior and lateral walls, respectively, of the left ventricular myocardium, and unipolar electrograms were recorded from the two locations simultaneously. The right femoral artery and both jugular veins were cannulated with large bore tubing. The venous return from the jugular veins and the femoral arterial return were joined by a Y cannula to a coronary arterial inflow catheter and tubing and passed through an occlusive Sarnes roller pump. A schematic diagram of the preparation is illustrated in Figure 1.

Venous or arterial inflow was selected by clamping the respective inflow line. The pump was calibrated for flow rates of 10 to 50 cc/min using timed collections of blood. The proximal segment of the anterior descending branch of the left coronary artery was dissected free and cannulated with a plastic no. 5F catheter as close as possible to its origin from the main left coronary artery. Blood PO_2 was measured with the Astrup method. The coronary artery initially was perfused by arterial blood with a PO_2 of 80 to 120 mm Hg. Flow was maintained at a rate that produced a mean perfusion pressure equal to a simultaneously recorded mean aortic pressure. Pressures were measured using Statham P23 Db pressure transducers. Aortic pressure, perfusion pressure and the two epicardial electrograms were recorded simultaneously on a direct-writing Hewlett Packard physiologic recorder. Flow was not altered thereafter.

Regional myocardial hypoxia was produced by perfusing the left anterior descending coronary artery by jugular venous blood with a PO_2 of 25 to 35 mm Hg. Hypoxia was considered present when the S-T segment was elevated at least 5 to 6 mm above the control level and myocardial cyanosis was observed in the distribution of the left anterior descending coronary artery. In six of the eight dogs studied, 6 mc of ^{129}Cs was injected into the inferior vena cava after induction of hypoxemia. Hypoxemia was maintained until scintigrams in three views (anterior, left anterior oblique and left lateral) were obtained. Scintigraphy was started 15 to 20 minutes after administration of ^{129}Cs, and 5 to 10 minutes was required to obtain each scintigram. Coronary perfusion with venous blood then was discontinued and femoral arterial perfusion was reinstituted. The hypoxic state was considered to have reverted to normal on disappearance of both S-T segment elevation and myocardial cyanosis, which occurred 5 to 15 minutes after arterial reperfusion. Serial scintigrams were obtained every 15 minutes for 180 minutes in the view in which the defect was most easily visualized. After this period repeat scintigrams in the other two views were obtained.

The remaining two dogs were studied in a different manner to evaluate the possibility that the scintigraphically observed defect was related to excessive efflux of ^{129}Cs from

TABLE I

Summary of Results in Seven Patients

Case no.	Graded Exercise Test	Resting ECG	Coronary Stenosis on Angiogram	Left Ventriculogram	Exercise ^{129}Cs Scintigram
1	Ischemic	No infarct	LCA, 50%; LAD, 75%; LCx, 75%; RCA, 90%	Normal	No defect
2	Ischemic	No infarct	LAD, 70%; LCx, 35%; RCA, 55%	Not performed	No defect
3	Ischemic	No infarct	RCA, 90%	Normal	No defect
4	Ischemic	Inferior infarct	LAD, 60%; LCx; 70% RCA, 80%	Generalized hypokinesia, akinesia of apex	No change in control defect
5	Ischemic	No infarct	LCx, 100%	Not performed	No defect
6	Ischemic	No infarct	LAD, 65%; RCA, 45%	Generalized hypokinesia	No defect
7	Ischemic	No infarct	LAD, 65%	Normal	No defect

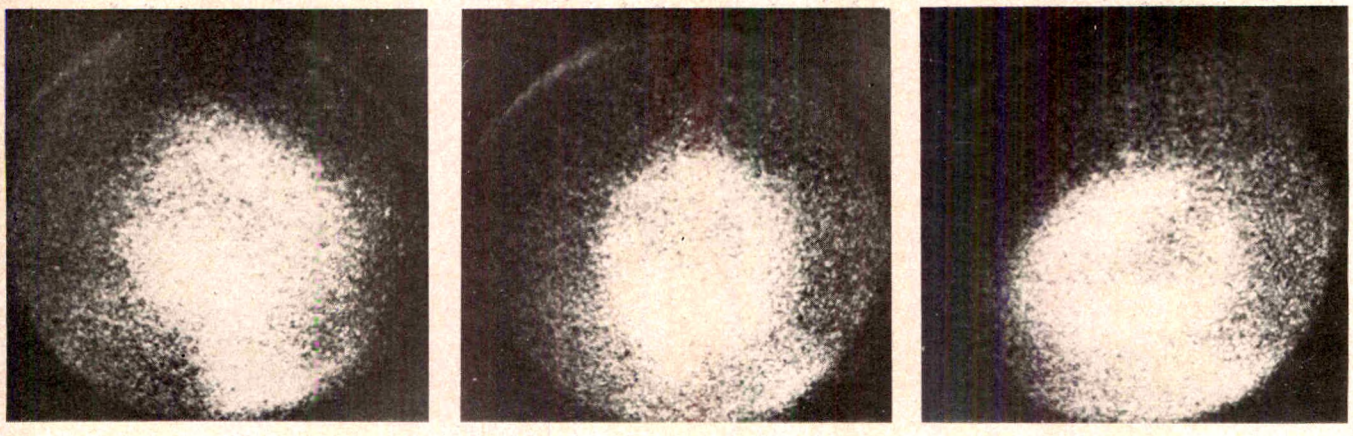
ECG = electrocardiogram; LAD = anterior descending branch of the left coronary artery; LCA = left main coronary artery; LCx = circumflex branch of the left coronary artery; RCA = right coronary artery.

the myocardial cells. In these two dogs the same preparation was utilized but ^{129}Cs was administered during the initial femoral arterial perfusion of the left anterior descending coronary artery and three control scintigrams were obtained. The left anterior descending coronary artery was then perfused with jugular venous blood for 180 minutes, and scintigrams were obtained in the anterior view every 15 minutes. After 180 minutes repeat scintigrams in all three views were obtained. The recordings were interpreted by two independent investigators experienced in interpreting myocardial scintigrams.

Results

Clinical Findings

The appearance of normal myocardial scintigrams obtained with use of intravenously administered ^{129}Cs has previously been described in detail.[3] There is an even uptake of ^{129}Cs by the myocardium, which



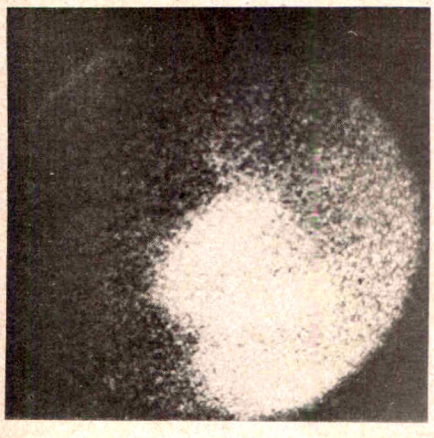


FIGURE 2. Case 5. Normal myocardial scintigram after exercise of a male patient without clinical or electrocardiographic evidence of myocardial infarction. ANT. = anterior view; LAO = left anterior oblique view; L.Lat. = left lateral view; LPO = left posterior oblique view.

FIGURE 3. Dog 2. Normal myocardial scintigram obtained before production of hypoxemia.

resembles a horseshoe or doughnut in the various views. Figures 2 and 3 are normal scintigrams from a patient (Case 5) and a dog, respectively. In the center of each scintigram there is a region of decreased to absent activity that represents the left ventricular cavity. The right ventricle is seen in some scintigrams as a thin wall that extends from the superior aspect of the interventricular septum.

In one of the seven patients (Case 4) with documented coronary artery disease, an area of decreased activity in the myocardial scintigram taken after exercise was identical to that activity observed in the control scintigram taken at rest. The patient's electrocardiogram revealed an old inferior wall myocardial infarction. Thus, none of our patients had areas of decreased activity in the myocardial scintigram that could be attributed to exercise-induced myocardial ischemia (Table I).

Experimental Findings

Each of the six dogs given ^{129}Cs before production of regional myocardial hypoxemia had an area of decreased to absent activity in the myocardial scintigram during hypoxia. The defect was present in one or all of the views taken and involved the apex and anterior wall of the left ventricle (Fig. 4). The defect in the scintigram corresponded to the area that was cyanotic when perfused with venous blood. Scintigrams in five of the six dogs demonstrated complete resolution of the defect 60 to 180 minutes after reinstitution of arterial perfusion. In the remaining dog partial resolution of the defect was observed in the lateral view but complete resolution in the left anterior oblique and anterior views. In contrast, the two dogs that received ^{129}Cs before the production of hypoxia did not manifest scintigraphic defects after 180 minutes of perfusion with hypoxemic venous blood.

Discussion

Myocardial scintigraphy using ^{129}Cs and a gamma camera has been shown to be a safe, simple and effective method for detecting an acute or old myocardial infarction.[3] In previous studies a myocardial infarction appeared in the scintigram as a defect or area of decreased to absent scintillations interrupting the smooth horseshoe or doughnut-shaped contour of the left ventricle. This study revealed that hypoxemia causes identical defects in the scintigram, and Zaret et al.[2] have shown similar results in exercise-induced myocardial ischemia.

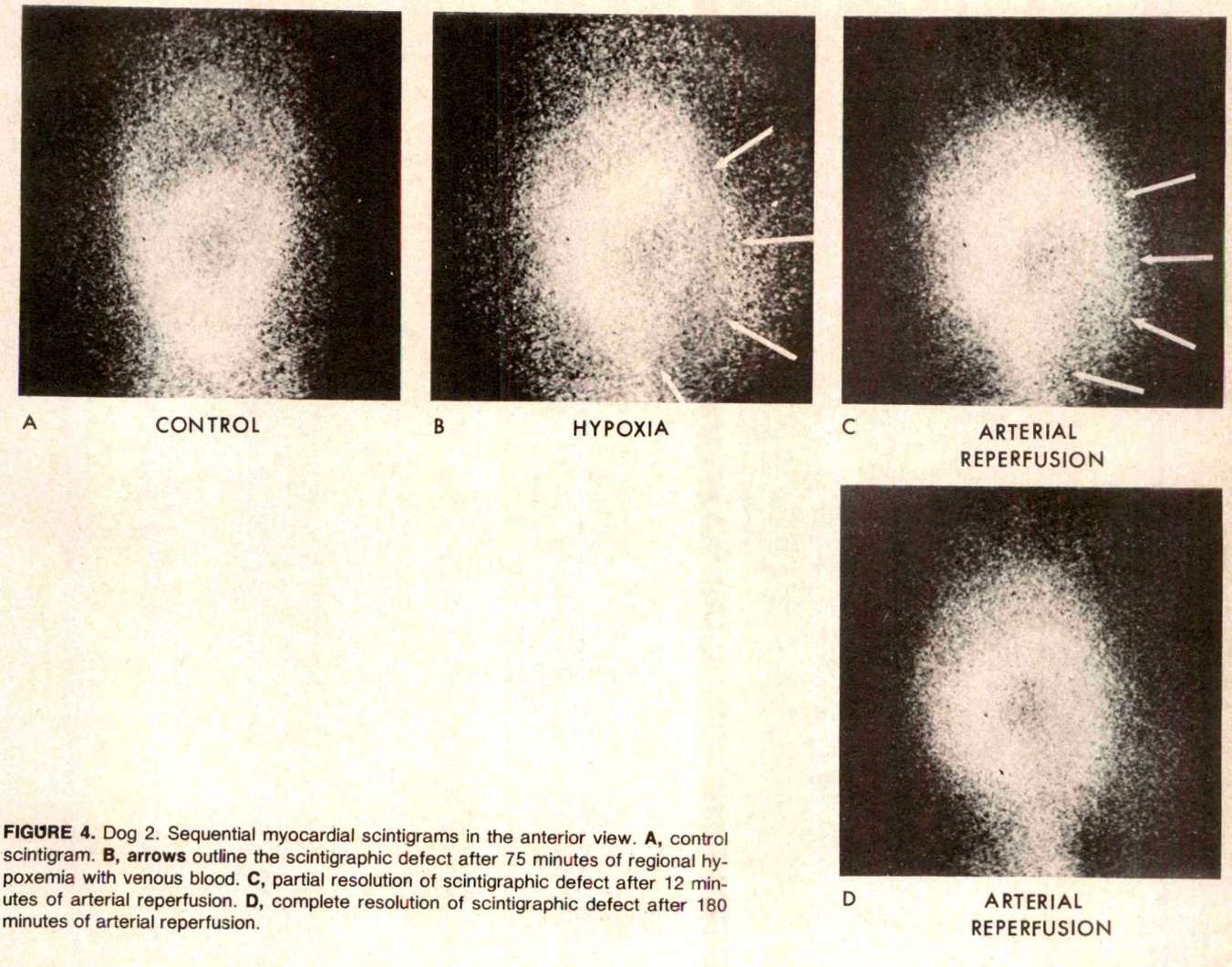


FIGURE 4. Dog 2. Sequential myocardial scintigrams in the anterior view. **A,** control scintigram. **B, arrows** outline the scintigraphic defect after 75 minutes of regional hypoxemia with venous blood. **C,** partial resolution of scintigraphic defect after 12 minutes of arterial reperfusion. **D,** complete resolution of scintigraphic defect after 180 minutes of arterial reperfusion.

Scintigraphic effect of hypoxia: A defect appearing in the scintigram could result from any or all of the following mechanisms in coronary artery disease: (1) inadequate perfusion, so that less radionuclide is presented to a portion of the myocardium than to surrounding regions that have a normal blood supply; (2) increased cellular permeability induced by hypoxia resulting in a net efflux of radionuclide from the myocardial cells; and (3) decreased cellular uptake of radionuclide secondary to damage of active transport mechanisms.

We have demonstrated that in the presence of severe regional myocardial hypoxia with adequate perfusion of that region ensured by controlled flow, the concentration of ^{129}Cs in the hypoxic region of the myocardium was decreased. A defect did not develop during 180 minutes of regional hypoxia in the two dogs that received ^{129}Cs before the induction of hypoxia. The inability to produce defects in these two dogs suggests that the most important cause of scintigraphically observed defects during hypoxemia is not excessive efflux of ^{129}Cs but decreased cellular uptake of ^{129}Cs secondary to damage to the active transport system of the myocardial cellular membrane.

Scintigraphic effect of exercise-induced ischemia: Each of the seven patients with an ischemic response to an exercise test and at least 50 percent narrowing of one major coronary artery demonstrated by coronary angiography had a normal exercise myocardial scintigram. This finding differs from the data of Zaret et al.,[2] who reported regions of decreased ^{43}K uptake with exercise in 16 of 19 patients with angina pectoris and positive coronary angiograms. Poe[10] reported that the myocardial uptake and clearance of potassium were more rapid and efficient than the uptake and clearance of cesium; however, the maximal myocardial concentration of the two radionuclides was the same. After intracoronary injection, potassium was more efficiently removed from the blood by the myocardium in a single passage than was cesium (71 percent versus 22 percent). Thus, ^{43}K scanning can commence within 5 to 10 minutes after intravenous administration, whereas with use of cesium a delay of 30 to 90 minutes is required to attain maximal counting rates although adequate scintigrams may be obtained within 10 to 15 minutes. The difference between the effects of regional hypoxia in the dog model and exercise-induced regional ischemia in man probably resulted from the delayed myocardial uptake of ^{129}Cs. The period of hypoxia in dogs was sufficiently prolonged to permit differentiation of ^{129}Cs in normal and hypoxemic myocardium. After resolution of hypoxic injury to the myocardial cell there was sufficient circulating ^{129}Cs available for resolution of the scintigraphic defect. In exercising man, although ^{129}Cs was given during the exercise-induced ischemic episode and scintigrams were obtained within 10 minutes of intravenous injection and termination of exercise, the ischemic state was dissipated before significant amounts of ^{129}Cs were cleared from the blood and concentrated by the myocardium. The rapid myocardial uptake and concentration of ^{43}K make it the agent of choice for evaluation of transient regional myocardial ischemia during exercise in patients with ischemic heart disease.

The effects of ischemia on the kinetics of potassium have been studied both experimentally in the dog[11] and in pacing-induced angina pectoris in man.[12] We could find no previous reports relating to the kinetics of cesium during ischemia. Case[11] has shown that the efflux of potassium from the ischemic myocardium was dependent on the magnitude and duration of the ischemia. Ischemia differs from hypoxia in that, although reduced oxygen tension is common to both states, perfusion is inadequate in the former. Decreased substrate delivery or retention of anaerobic metabolites, or both, could affect membrane permeability adversely in the ischemic model. Therefore, our studies of regional myocardial hypoxemia in dogs are not entirely applicable to acute myocardial infarction, acute coronary insufficiency or exercise-induced angina pectoris in man. Nevertheless, we have shown that a major cause for a myocardial defect observed in scintigrams obtained with ^{129}Cs is inadequate myocardial uptake by the hypoxic cell in the presence of adequate perfusion.

In addition, the presence of a scintigraphically observed defect in both experimental myocardial hypoxia and in exercise-induced ischemia in studies using ^{43}K[2] suggests that the size of an acute myocardial infarct may be overestimated by myocardial scintigraphy. This discrepancy does not depend upon the physiologic mechanism that causes the scintigraphic defect. Ultimately the sensitivity of myocardial scintigraphy in quantitating the size of an acute myocardial infarct will require correlation with postmortem examination of the heart.

Acknowledgment

We are grateful for the support and assistance given by Dr. R. O. Bondelid, Mr. R. B. Theus, Mr. G. E. Miller and the Operation Section of the Cyclotron Branch of the Naval Research Laboratory, Washington, DC., for the production of the ^{129}Cs used in this project; by Richard Grant of the Nuclear Medicine Laboratory for the extraction and preparation of the ^{129}Cs and by Jeannine Lewis and Tim Cahill of the Nuclear Medicine Laboratory for their assistance in obtaining the myocardial scans.

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Ventricular Performance in Patients Based Upon Rate of Change of Power During Isovolumic Contraction

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Energy is expended by the ventricle during isovolumic contraction as the blood within the ventricle is compressed. This isovolumic energy of compression, as well as the isovolumic rate of energy transfer (power) and acceleration of energy transfer (rate of change of power), was calculated in 17 patients with angina pectoris who underwent diagnostic cardiac catheterization. The peak isovolumic rate of change of power in patients with normal left ventricular performance (based upon the ejection fraction, mean velocity of circumferential fiber shortening and end-diastolic volume index) was 31,000 ± 3,000 dynes cm sec^{-2} (mean ± standard error), whereas in those with poor ventricular performance it was 18,000 ± 2,000 dynes cm sec^{-2} (P <0.01). None of the patients with poor ventricular performance had a peak isovolumic rate of change of power that exceeded 25,000 dynes cm sec^{-2}. Overlap between patients with normal performance and those with reduced performance was less with the peak rate of change of power than with peak power, peak rate of change of intraventricular pressure (dp/dt), maximal (dp/dt)/p or Vmax. The derivation of these isovolumic energy transfer rates requires no assumptions related to ventricular geometry or characteristics of muscle fibers. Peak isovolumic rate of change of power may be a useful and sensitive indicator of ventricular performance in patients with coronary artery disease.

During the isovolumic portion of systole, as the ventricular muscle fibers tense before ejection, there is a small but theoretically measurable compression of the blood within the ventricle. Energy is expended by the ventricle as this occurs. This isovolumic energy expenditure is dependent upon end-diastolic volume and intraventricular pressure.[1] Of perhaps greater importance, the rate of energy expenditure (power) and acceleration of energy expenditure (rate of change of power) during isovolumic contraction can also be calculated on the basis of the principles utilized to determine isovolumic energy expenditure.[1] The ventricular rate of change of power during isovolumic contraction is dependent upon end-diastolic volume, intraventricular pressure, the rate of change of intraventricular pressure (dp/dt) and the acceleration of intraventricular pressure (d^2p/dt^2).[1] Each of these component terms of the rate of change of power, namely, end-diastolic volume, dp/dt and d^2p/dt^2, has empirically been shown to reflect ventricular performance. Therefore, it seems that the expression for the isovolumic rate of change of power, which combines these terms in a physiologically meaningful fashion, might be advantageous for the evaluation of cardiac function. No assumptions of ventricular geometry, fiber orientation or muscle mechanics are implicit in the derivation of the expression. Studies in dogs demonstrated that the peak rate of change of power during isovolumic contraction is sensitive to

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drug-induced alterations of the contractile state yet little affected by alterations in preload or afterload.[1]

The following attributes of the ventricular isovolumic rate of change of power recommend its further evaluation: (1) It expresses a physiologically meaningful concept. (2) It is based upon firm principles of fluid dynamics. (3) Its derivation is based upon no assumptions related to ventricular geometry or muscle mechanics. For these reasons, it has theoretical advantages over indexes of performance that are empirical or dependent upon various assumptions. Therefore, this study was undertaken to evaluate in patients the ventricular isovolumic rate of change of power.

Methods

Theoretical Considerations

The following derivations of the expressions for ventricular isovolumic energy, power and rate of change of power have been previously published in detail.[1] Because these derivations are important to the thoughtful application of these expressions, they are shown here.

The energy expended by the ventricle in the form of elastic compression of the blood during the isovolumic phase of systole can be described by utilizing the basic mathematical expression for work:

$$\text{Work} = \int p\, dV \qquad (1)$$

where p is intraventricular pressure (dynes cm^{-2}) and dV is a small change of ventricular volume (cm^3) and work is expressed in units of dynes cm.

The change in ventricular volume during isovolumic contraction is extremely small due to the relative incompressibility of blood. On the basis of the modulus of volume elasticity, this change of volume, dV, can be described as:

$$dV = -\frac{V_0}{M_B} dp \qquad (2)$$

where M_B is the isothermal modulus of volume elasticity (bulk modulus) of blood (2.25×10^{10} dynes cm^{-2})*, dp is a small change of pressure (dynes cm^{-2}) and V_0 is ventricular end-diastolic volume (cm^3).

Therefore, by combining Equations 1 and 2, the resulting expression for work (energy of compression) performed during isovolumic contraction is:

$$\text{Work} = -\frac{V_0}{M_B}\int_{p_1}^{p_2} p\, dp \qquad (3)$$

where p_1 is left ventricular end-diastolic pressure and p_2 is aortic diastolic pressure.†

The energy expended during a single isovolumic contraction can readily be calculated by solving Equation 3 and obtaining the following:

$$\text{Work} = \frac{V_0}{2M_B}(p^2_2 - p^2_1) \qquad (4)$$

The instantaneous rate of change of energy transfer, or power, is obtained by differentiation of Equation 3, which yields the following result:

$$\text{Power} = \frac{d(\text{work})}{dt} = -\frac{V_0}{M_B} p\, dp/dt \qquad (5)$$

where power is in dynes cm sec^{-1}.

Differentiation with respect to time of this expression for power, (Equation 5) results in an expression for the rate of change of power, which is:

$$\frac{d(\text{power})}{dt} = -\frac{V_0}{M_B}\left[\left(\frac{dp}{dt}\right)^2 + p\,\frac{d^2p}{dt^2}\right] \qquad (6)$$

where the rate of change of power is in units of dynes-cm sec^{-2}. The term d^2p/dt^2 indicates the acceleration of intraventricular pressure (dynes cm^{-2} sec^{-2}).

Studies in Patients

Isovolumic energy, power and rate of change of power were calculated in 17 patients who underwent diagnostic cardiac catheterization for the evaluation of angina pectoris. All but one had coronary artery disease of various degrees of severity; one had apparently normal coronary arteries. Patients with valvular disease were excluded. All patients received light sedation with diazepam (Valium®) and were studied in the postabsorptive state. Hemodynamic measurements were made before the injection of contrast material.

Pressures were measured with a catheter-tip micromanometer (Millar Instruments, Inc., Houston, Texas) that has a frequency response of 20 kilohertz (manufacturer's specifications). The catheter-tip pressure sensor was calibrated with a mercury manometer before each study. A zero base line was established at the beginning of each study and confirmed at the end of the study.

Pressures were recorded on a photographic recorder at a paper speed of 200 mm/sec. The pressures were manually digitized at 1 mm (0.005 second) intervals. Appropriate corrections were made for minor variations of the paper speed. Equations descriptive of left ventricular pressure were calculated by the Chebyshev polynomial approximation technique with the aid of a Hewlett Packard HP 2100A computer. Usually a 5th degree polynomial equation satisfactorily described the left ventricular pressures during the isovolumic period. Any points from the computed data that disagreed by 10 percent or more from measured data were discarded. Such points were almost always at the initial portion of the curves. Most portions of the curves were within 3 percent of the digitized data. From the computed mathematical equations descriptive of intraventricular pressure, the instantaneous first and second derivatives of pressure, (dp/dt)/p, power and the rate of change of power were calculated at 5 msec intervals throughout the entire isovolumic period.* Two or more beats were analyzed during control periods and after each intervention, and the results were averaged. End-diastolic volume, a factor in the isovolumic energy of compression, power and rate of change of power, was measured by ventriculography (as

* The bulk modulus of blood was assumed to be the same as that of water at 37° C.[2]

† The negative sign in the equation for work, power and rate of change of power during the isovolumic period indicates that energy is being transferred from the heart to the blood. For practical application of the expression, the minus sign is usually neglected.

* Calculation of the ratio of dp/dt to p by utilization of instantaneous values obtained from the digitized pressure curve eliminates errors related to time delays in circuitry of many resistance-capacitance differentiators. Slight time delays due to resistance-capacitance differentiators would cause this ratio to be lower than that calculated by the more precise methods in this study.

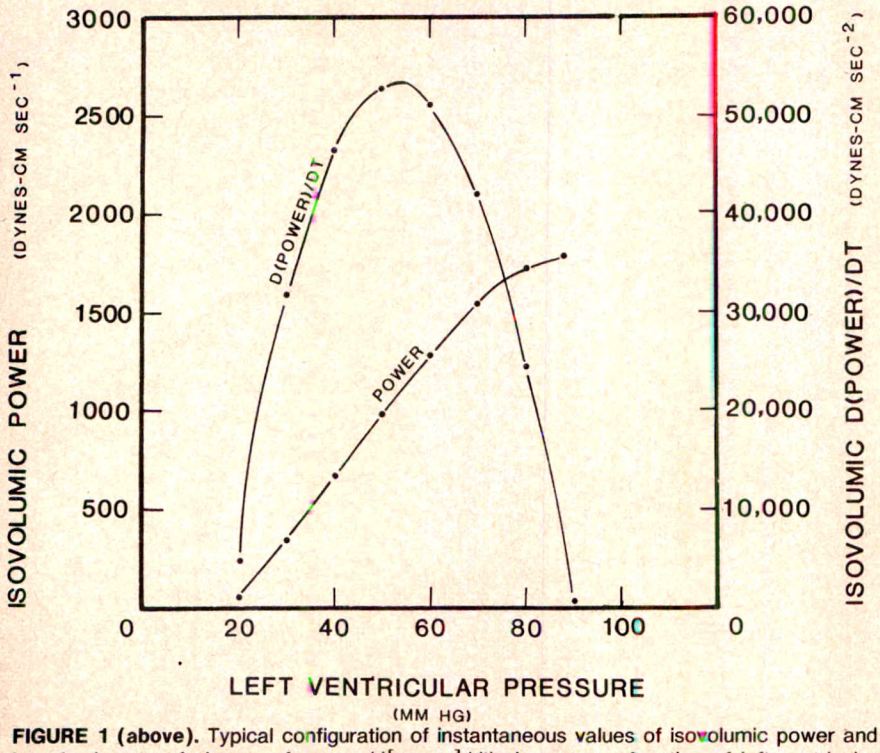

FIGURE 1 (above). Typical configuration of instantaneous values of isovolumic power and isovolumic rate of change of power (d[power]/dt) shown as a function of left ventricular pressure. Power reached a peak at the end of the isovolumic period. The rate of change of power reached a peak during the mid-portion of isovolumic contraction. (This patient had an ejection fraction of 66 percent, a mean velocity of circumferential fiber shortening of 1.64 sec^{-1} and end-diastolic volume index of 54 cm^3/m^2.)

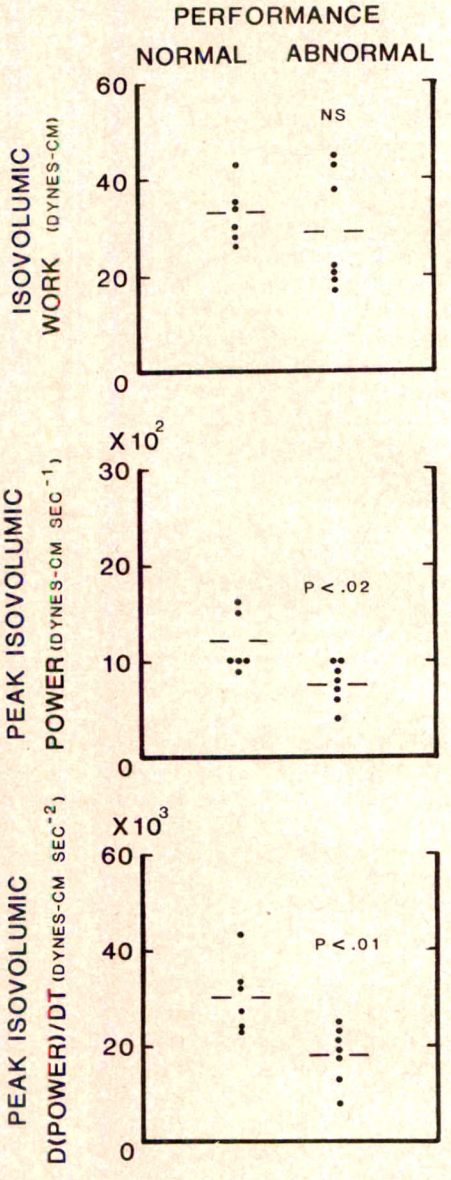

FIGURE 2 (right). Isovolumic work per beat **(top),** peak isovolumic power **(middle)** and peak isovolumic rate of change of power **(bottom)** in patients with normal and abnormal ventricular performance as characterized by ejection fraction, mean rate of circumferential fiber shortening and left ventricular end-diastolic volume index. The isovolumic rate of change of power showed the least overlap of values, and differed significantly in patients with normal performance and those with abnormal performance ($P < 0.01$). Values for isovolumic peak power in patients with normal ventricular performance also differed from values in patients with abnormal performance ($P < 0.02$); values for isovolumic energy transfer (work) did not differ (NS).

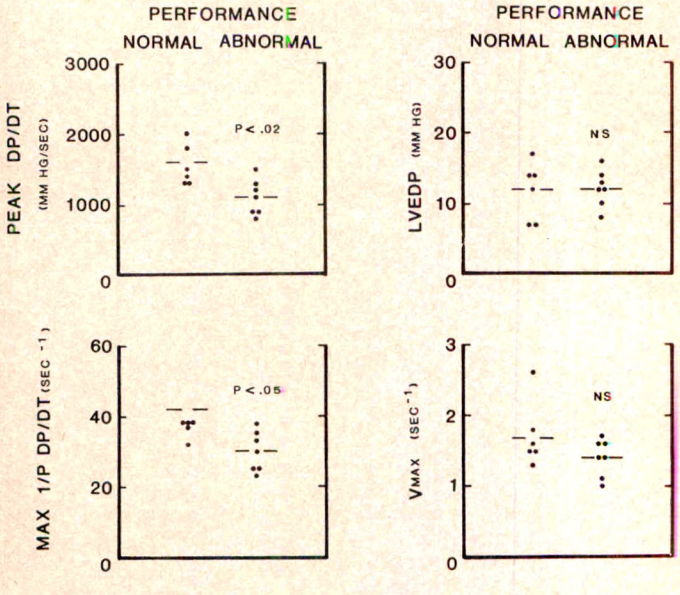

FIGURE 3. Left ventricular peak dp/dt **(top left),** maximal (dp/dt)/p **(lower left),** left ventricular end-diastolic pressure (LVEDP) **(top right),** and Vmax **(lower right)** in patients with normal left ventricular performance and those with abnormal performance. Although left ventricular peak dp/dt and maximal (dp/dt)/p in patients with normal performance differed significantly from values in those with abnormal performance, there was a wide overlap. Vmax and left ventricular end-diastolic pressure revealed no significant differences between groups.

will be described), and this result was also entered into the computer program.

Vmax was calculated as the linear extrapolation of dp/dt/32p plotted with respect to intraventricular pressure.[3] Data corresponding to pressures of less than 20 mm Hg were excluded because of inherent inaccuracies related to calculations of ratios of small numbers. Both Vmax and maximal dp/dt/p were calculated on the basis of the actual pressure.[3,4]

A ventriculogram was obtained after the measurement of control pressures, and left ventricular end-diastolic volume was calculated by the single plane area-length method.[5] Ventriculograms were recorded on 35 mm cine film at 64 frames/sec during the injection of 40 cm^3 of sodium and meglumine diatrizoates (Hypaque M®, 75 percent). Amplification was determined by utilization of a two-dimensional scale that also permitted compensation for any roentgenographic distortion. Such distortion was negligible. Only the first four beats of each injection were analyzed to avoid possible alterations of contractility due to contrast material passing through the coronary circulation. Care was taken to exclude from the study any patients whose ventriculograms revealed premature ventricular contractions. The ejection fraction was calculated from the ventriculogram as the ratio between the volume ejected and end-diastolic volume.

Categorization of ventricular performance: Patients were categorized as having normal ventricular performance if they had an ejection fraction[6,7] greater than 58 percent, a mean velocity of circumferential fiber shortening[8] greater than 1.30 sec^{-1} and a left ventricular end-diastolic volume index[6,7] of less than 90 cm^3/m^2. There were six such patients. Seven patients, categorized as having abnormal ventricular performance, had an ejection fraction[9] of less than 50 percent and a mean velocity of circumferential fiber shortening[8] of less than 1.0 sec^{-1}. The criteria for normal values for ejection fraction and mean velocity of circumferential fiber shortening were stringent. Values in intermediate ranges in which others have reported an overlap between normal and abnormal data, were excluded. Four additional patients had either intermediate or discordant values for ejection fraction and mean velocity of circumferential fiber shortening. The data from these patients were included in regression analyses but were excluded from comparisons of patients with normal and abnormal performance.

Results

Ventricular power during isovolumic contraction starts from a low value and reaches a peak at the end of the isovolumic period; the rate of change of power reaches a peak earlier during the isovolumic period than peak power (Fig. 1).

The peak rate of change of power during isovolumic contraction in patients with normal ventricular performance (as characterized by the ejection fraction, mean velocity of circumferential fiber shortening and end-diastolic volume index) was 31,000 ± 3,000 dynes cm sec^{-2} (mean ± standard error), whereas in patients with abnormal performance, the peak rate of change of power was 18,000 ± 2,000 dynes cm sec^{-2} (P <0.01).* Overlap of values between patients with normal ventricular performance and those with poor ventricular performance was less with the peak rate of change of power than with any of the other measured isovolumic indexes of performance (Fig. 2 and 3). Values for peak rate of change of power greater than 25,000 dynes cm sec^{-2} were observed only in patients with normal ventricular function (Fig. 2). The isovolumic peak rate of change of power correlated approximately with the left ventricular peak rate of change of pressure (r = 0.67)† (Fig. 4). The peak rate of change of power correlated less well with the ejection fraction (r = 0.49) (Fig. 5) and with the mean velocity of circumferential fiber shortening (r = 0.42) (Fig. 6).

Peak power during isovolumic contraction was 1,200 ± 100 dynes cm sec^{-1} in patients with normal ventricular performance. It was 800 ± 100 dynes cm sec^{-1} in those with poor ventricular function (P <0.02) (Fig. 2).

Isovolumic energy transfer per beat did not differ significantly in patients with normal performance (33 ± 2 dynes cm) and those with abnormal performance (29 ± 5 dynes cm) (Fig. 2).

* Unpaired t test.
† r = correlation coefficient.

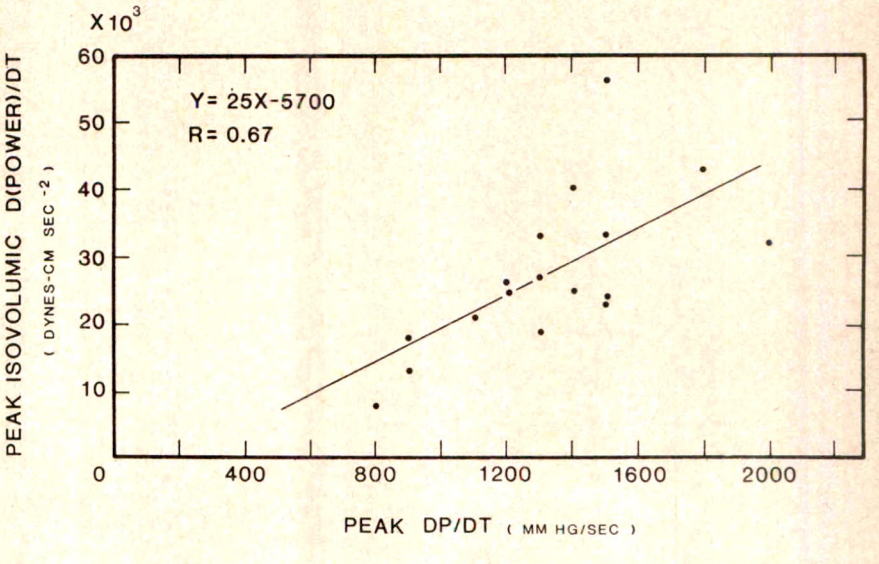

FIGURE 4. Isovolumic rate of change of power (d[power]/dt) shown as a function of left ventricular peak rate of change of pressure (dp/dt). Regression equation and correlation coefficient (R) are shown.

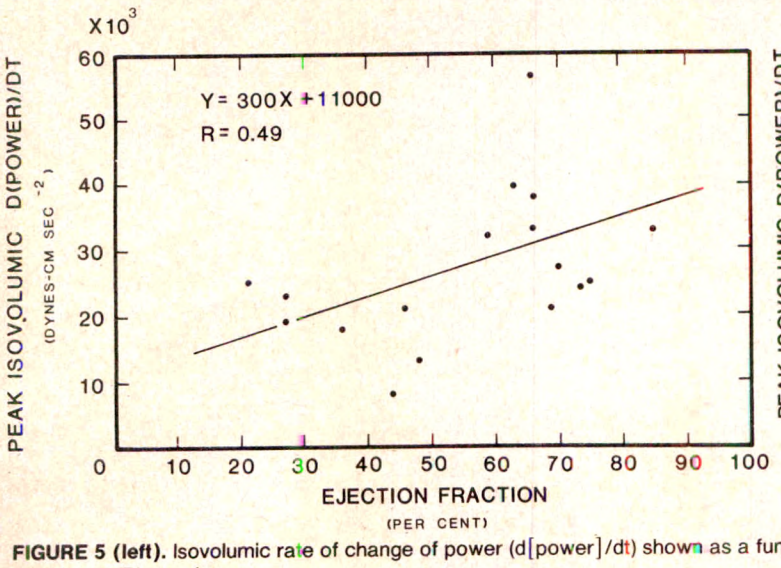

FIGURE 5 (left). Isovolumic rate of change of power (d[power]/dt) shown as a function of ejection fraction. Regression equation and correlation coefficient (R) are shown.

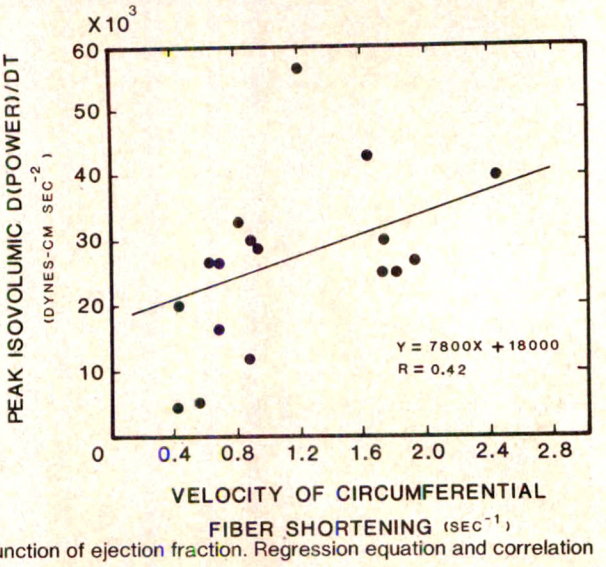

FIGURE 6 (right). Isovolumic peak rate of change of power (d[power]/dt) shown as a function of the mean velocity of circumferential fiber shortening (mean V_{CF}). Regression equation and correlation coefficient (R) are shown.

Nearly all of the patients had normal values for left ventricular peak dp/dt[10] irrespective of ejection fraction or mean velocity of circumferential fiber shortening (Fig. 3). However, there was a significant difference between values in patients with normal and poor ventricular performance ($P < 0.02$). Even though the means differed, there was a wide overlap of values (Fig. 3). There was also a wide overlap of values of maximal (dp/dt)/p between those in whom the ejection fraction and velocity of circumferential fiber shortening were normal and those in whom they were reduced (Fig. 3). Values for Vmax were comparable in patients with apparently normal ventricular performance and in those with poor ventricular function. A good correlation between the isovolumic peak rate of change of power would therefore not be expected. There was, in fact, no correlation of the peak isovolumic rate of change of power with maximal (dp/dt)/p ($r = 0.20$) or Vmax ($r = 0.22$).

Discussion

Just as the rate of change of power appears to be a meaningful index of performance during ejection,[11,12] the rate of change of power may also be a meaningful index of performance during the isovolumic period.[1] The peak isovolumic rate of change of power clearly reflects alterations of ventricular performance even though its value is small in comparison with values for peak power and the peak rate of change of power during ejection. Since the isovolumic rate of change of power is a function of end-diastolic volume, rate of change of intraventricular pressure and acceleration of intraventricular pressure, the inclusion of these terms, previously found to be of empirical value for the evaluation of ventricular performance, predictably would cause this expression to reflect the contractile state.

Usefulness of peak isovolumic rate of change of power as index of ventricular performance: Because of its theoretical validity and its physiologic meaning, the peak isovolumic rate of change of power has attributes that recommend its utilization as an index of ventricular performance and, in this role, appears to be more useful than peak power. There was less overlap of values in peak isovolumic rate of change of power in patients with normal or reduced ventricular performance than was observed with peak isovolumic power. Studies in dogs[1] showed that the peak rate of change of power prominently reflected changes in contractile state yet was insensitive to changes in afterload, and was not affected in a statistically significant fashion by changes in preload. Peak isovolumic power in dogs was less responsive to a drug-induced augmentation of the contractile state and, in contradistinction to the rate of change of power, was affected by alterations in preload.[1]

Considerations and assumptions in derivation of equations: The derivation of the rate of change of power is based upon considerations of the energy transferred to the blood in the form of elastic compression. That is, only the energy expended by the ventricle that is actually utilized for elastic compression is calculated. The total production of energy by the ventricle during the isovolumic period is not considered in these energy transfer equations; nor is energy storage within the series elastic a factor. Contractile element work during isovolumic contraction has been calculated by Britman and Levine.[13]

The only assumption implicit in the derivation of equations representative of the isovolumic energy of compression, power and rate of change of power, is that of isothermal conditions during the isovolumic

period. On the basis of the assumption of no change in temperature of the blood within the ventricle during the isovolumic period, one is permitted to utilize the isothermal modulus of elastic compressibility. During the entire ejection period, the increase in temperature in the left ventricle is approximately 0.01° C.[14] During isovolumic contraction, the energy expenditure of the ventricle is much less than during ejection. Therefore, the heat production, and the induced change in temperature of the blood within the ventricle during isovolumic contraction would be much less than 0.01° C. Such infinitesimal changes in temperature permit utilization of the isothermal modulus of elastic compressibility.[2]

Since the exact value of the bulk modulus for blood is not known, computations in this study were based upon the value of the bulk modulus of water at 37° C.[2] Any errors due to a possible difference between the isothermal modulus of volume elasticity of blood and of water would be constant for all calculations. That is, any possible variation between the results reported in this study and more precise values based upon a measured bulk modulus of blood would differ only by an unchanging and presumably small factor.

No assumptions are implied in regard to the synergy of isovolumic contraction, uniformity of muscle fiber orientation, ventricular geometry or the elasticity of muscle fibers. The avoidance of these assumptions gives the method an advantage over indexes that attempt to apply theories of muscle mechanics to the contractile state of the heart.[15] Although the shape of the ventricle changes somewhat during isovolumic contraction, even in patients without mitral regurgitation,[16] such a change of shape would not affect the theoretical validity of the derived expressions. Since all calculations presume a truly isovolumic period, it is necessary to assume a nonregurgitant atrioventricular valve.

The change in volume that the blood undergoes within the ventricle is small. Assuming an end-diastolic volume of 150 cm^3 and a typical change in pressure of 70 mm Hg (the difference between aortic diastolic pressure and left ventricular end-diastolic pressure) the change in blood volume within the ventricle would be 6×10^{-4} cm^3, as calculated from Equation 3.

Clinical implications: The peak isovolumic rate of change of power, as well as peak isovolumic power, in patients with angina pectoris permitted distinction between those with normal or poor left ventricular performance. Values for peak isovolumic rate of change of power showed less overlap between those with normal and abnormal performance than did those for peak isovolumic power. Normal values for peak dp/dt were measured in nearly all patients, irrespective of ventricular function. Because of its theoretical validity, its physiologic meaning and its ready applicability, the peak isovolumic rate of change of power appears to be a useful and practical expression in evaluating ventricular performance.

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Isovolumic Fractional Rate of Change of Power: Its Applicability to Assessment of Ventricular Performance in Patients

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The ratio of the instantaneous isovolumic rate of change of power, normalized to instantaneous isovolumic power, appears to be an expression of physiologic and practical significance. This ratio, termed the isovolumic fractional rate of change of power, describes the capability of the ventricle to sustain, during isovolumic contraction, an acceleration of energy production relative to instantaneous rates of energy production. The expression is independent of assumptions of ventricular geometry, fiber orientation, symmetry of contraction or elasticity of muscle fibers. It was derived upon the basis of established principles of fluid dynamics. The expression serves in an integrative fashion by demonstrating a simple relation between characteristics of performance derived on the basis of fluid dynamics and those derived on the basis of muscle mechanics. In this study, the isovolumic fractional rate of change of power permitted distinction between patients with normal and abnormal ventricular performance (as characterized by the ejection fraction, mean velocity of circumferential fiber shortening and end-diastolic volume index) ($P < 0.01$). The firm theoretical basis of the isovolumic fractional rate of change of power, and its demonstrated capability to permit identification of patients with normal or abnormal left ventricular performance, recommends it as a meaningful and useful hemodynamic expression.

The peak acceleration of energy generated by the ventricle during isovolumic contraction (peak isovolumic rate of change of power) was shown in dogs to be sensitive to drug-induced alterations in contractile state and little affected by alterations in preload or afterload.[1] In patients with angina pectoris it permitted distinction between those with normal or abnormal left ventricular performance.[2] The peak isovolumic rate of change of power has theoretical and physiologic merits that recommend its utilization for the evaluation of ventricular performance. However, the need to measure ventricular end-diastolic volume diminishes the applicability of this expression for repetitive measurements. For this reason, an expression closely related to the isovolumic rate of change of ventricular power was derived to circumvent this need. This expression, which we term the isovolumic fractional rate of change of ventricular power, represents the rate of change of ventricular power relative to instantaneous power developed during isovolumic contraction. It is calculated as the ratio of the isovolumic rate of change of power to isovolumic power. As will be shown in the following derivations, end-diastolic volume, a constant factor in both the isovolumic rate of change of power and isovolumic power, cancels from the final expression.

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Studies in dogs show that the fractional rate of change of power is sensitive to drug-induced alterations of the contractile state, yet is affected insignificantly by variations in preload or afterload.[3] In this study, the fractional rate of change of power was investigated in patients with angina pectoris who underwent diagnostic cardiac catheterization.

Methods

Derivation of Equations

The rate of ventricular energy transfer (power) during isovolumic contraction has been determined to be dependent upon intraventricular pressure (p), rate of change of pressure (dp/dt), end-diastolic volume (V_0) and the bulk modulus of blood (M_B)[1,2]:

$$\text{Isovolumic Power} = -\frac{V_0}{M_B} p \, dp/dt \qquad (1)$$

where power is expressed in units of dynes cm sec^{-1}, pressure in dynes cm^{-2}, dp/dt in dynes cm^{-2} sec^{-1} and volume in cm^3.

Differentiation with respect to time of this expression for isovolumic power (Equation 1) results in an expression for rate of change of power, which is:

$$\frac{d(\text{power})}{dt} = -\frac{V_0}{M_B}\left[\left(\frac{dp}{dt}\right)^2 + p\,\frac{d^2p}{dt^2}\right] \qquad (2)$$

where the rate of change of power is in units of dynes cm sec^{-2}. The term d^2p/dt^2 indicates the acceleration of intraventricular pressure (dynes $cm^{-2}sec^{-2}$).

The fractional rate of change of power (FRCP) is obtained by dividing the rate of change of power by power (Equation 2 divided by Equation 1):

$$\text{FRCP} = \frac{1}{P}\frac{dP}{dt} = \frac{1}{p}\frac{dp}{dt} + \frac{1}{\dot{p}}\frac{d\dot{p}}{dt} \qquad (3)$$

where **P** is power; d**P**/dt is rate of change of power; $\dot{p}$ is identical to dp/dt; and $d\dot{p}/dt$ is identical to d^2p/dt^2.

The fractional rate of change of power is a nearly nondimensional term with units of sec^{-1}. It is descriptive of the rate of change of power relative to the instantaneous power. It is more readily measured than the rate of change of power, since end-diastolic volume is not a factor in this expression. The bulk modulus of blood (M_B) also is canceled from the equation.

Studies in Patients

The isovolumic fractional rate of change of ventricular power was calculated in the 17 patients who underwent diagnostic cardiac catheterization for the evaluation of angina pectoris (as described in the preceding paper[2]). All but one of the patients had coronary artery disease of various degrees of severity; one patient had normal coronary arteries. Patients with valvular disease were excluded. All patients received light sedation with diazepam (Valium®) and were studied in the postabsorbtive state.

Pressures were measured with a high frequency micromanometer (Millar Instruments, Inc., Houston, Texas) located at the tip of a cardiac catheter. The pressures were manually digitized, and equations descriptive of left ventricular pressure were calculated by the Chebyshev polynomial approximation technique as previously described.[1,2] From the computed mathematical equations descriptive of intraventricular pressure, the instantaneous first and second derivatives of pressure, dp/dt/p and the fractional rate of change of power were calculated at 5 msec intervals throughout the isovolumic period. Maximal velocity of contractile element shortening, Vmax, was calculated as the linear extrapolation of (1/32p)(dp/dt) plotted with respect to intraventricular pressure.[4] Both Vmax and maximal dp/dt/p were calculated on the basis of total pressure.[4,5]

The isovolumic fractional rate of change of power was measured at various arbitrarily selected values of intraventricular pressure. Values of the fractional rate of change of power at intraventricular pressures between 50 and 65 mm Hg were found to be convenient for purposes of describing the data. As will be shown in the Results, a readily measurable peak value of the fractional rate of change of power did not occur. Because of the inaccuracies related to computations of the ratios of small numbers, the fractional rate of change of power was not computed during the initial portion of isovolumic contraction.

After the measurement of intraventricular pressure, a ventriculogram was obtained, as previously described,[2] from which left ventricular volumes were calculated by the single plane area-length method. The ejection fraction was calculated from the ventriculograms as the ratio of the volume ejected to end-diastolic volume. Utilizing the ventriculographically measured volume, the isovolumic rate of change of ventricular power was also calculated at 5 msec intervals.[2]

Categorization of patients: Patients were categorized as described previously.[2] Six had normal ventricular performance (ejection fraction greater than 58 percent and a mean velocity of circumferential fiber shortening greater than 1.3 sec^{-1} in the presence of a left ventricular end-diastolic volume index of less than 90 cm^3/m^2). Seven patients had abnormal ventricular performance (ejection fraction less than 50 percent and mean velocity of circumferential fiber shortening less than 1.0 sec^{-1}). There were four additional patients with either intermediate or discordant values for ejection fraction and mean velocity of circumferential fiber shortening whose data were included in regression analyses but excluded from comparisons of patients with normal and abnormal ventricular performance.

Results

The fractional rate of change of power steadily diminished after the first few milliseconds of isovolumic contraction. Its typical configuration is shown in Figure 1. A peak value did not occur. The fractional rate of change of power was higher at various levels of intraventricular pressure in patients with a normal ejection fraction and velocity of circumferential fiber shortening than in patients with a diminished ejection fraction or fiber shortening rate (Fig. 1 and 2). This finding indicates that such patients had higher levels of the rate of change of power, relative to instantaneous power, throughout most of the isovolumic period. It therefore appears that the ventricle of a patient with normal performance was able to generate a greater rate of change of power relative to any instantaneous value of isovolumic power and could sustain this higher fractional increment of power throughout the isovolumic period.

The fractional rate of change of power measured at a ventricular pressure of 55 mm Hg was 32 ± 4 sec^{-1} in patients with normal ventricular performance,

whereas it was 16 ± 4 sec^{-1} in patients with poor ventricular performance (P <0.01) (Fig. 2, Tables I and II). When measured at intraventricular pressures of 50, 60 and 65 mm Hg, the fractional rate of change of power also permitted distinction between patients with normal and abnormal ventricular performance (Fig. 2). There was some overlap between groups in value ranges for the fractional rate of change of power of 25 to 27 sec^{-1} when these values were measured, for example, at 55 mm Hg. However, when values were measured at this pressure level, no patients with poor ventricular performance had an isovolumic fractional rate of change of power greater than 27 sec^{-1} (Fig. 3, Tables I and II).

The isovolumic fractional rate of change of power, measured at 55 mm Hg, correlated with the isovolumic peak rate of change of power (r = 0.77) (Fig. 4). Correlation was less close (r = 0.60) (Fig. 5) with the velocity of circumferential fiber shortening and was poor (r = 0.42) (Fig. 6) with the ejection fraction.

Nearly all of the patients, irrespective of ejection fraction and mean velocity of circumferential fiber shortening, had a normal peak dp/dt (Tables I and II). Even though the means differed significantly (P

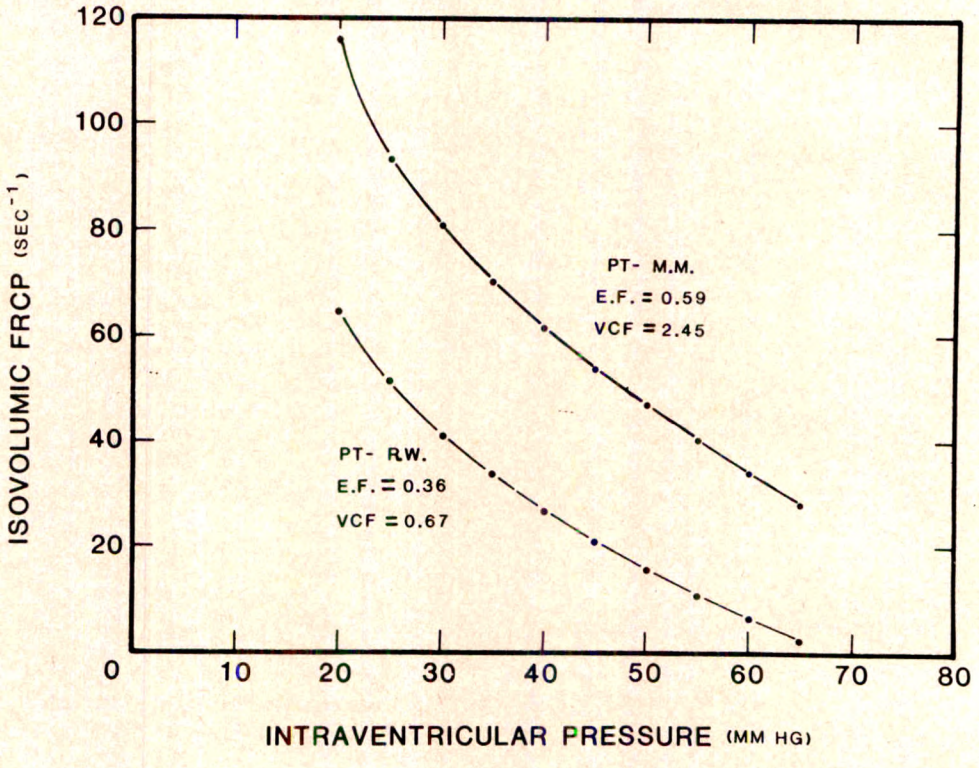


FIGURE 1. Instantaneous values of the isovolumic fractional rate of change of power (FRCP) shown as a function of intraventricular pressure. **Upper curve,** Patient 4 (M.M.), with an ejection fraction (E.F.) of 59 percent and a mean velocity of circumferential fiber shortening (VCF) of 2.45 sec^{-1}. **Lower curve,** Patient 11 (R.W.), with an ejection fraction of 36 percent and a mean velocity of circumferential fiber shortening of 0.67 sec^{-1}.

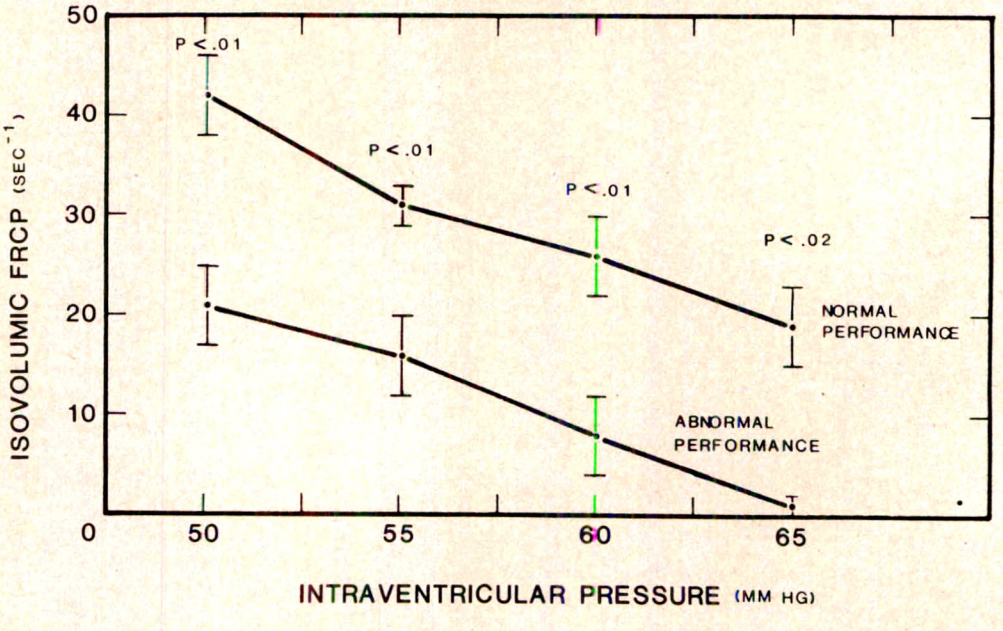


FIGURE 2. Isovolumic fractional rate of change of power (FRCP) in patients with normal ventricular performance **(upper line)** and poor ventricular performance **(lower line).** The differences between groups was significant irrespective of the pressure at which the isovolumic fractional rate of change of power was measured. (Values ± standard error are shown.)

TABLE I

Hemodynamic Variables in Patients with Normal Ventricular Performance Based Upon Ejection Fraction, Velocity of Circumferential Fiber Shortening and Left Ventricular End-Diastolic Volume Index

Case no.	HR	BP	CI	LVEDP	EF	V_{CF}	LVEDVI	Peak dp/dt (mm Hg/sec)	Maximal dp/dt / p	Vmax	FRCP
1	64	150/82	2.3	14	66	1.64	54	1800	38	1.67	46
2	60	120/77	2.8	17	75	1.73	61	1400	38	1.49	25
3	94	130/80	3.4	12	73	1.92	55	1500	38	1.59	27
4	92	127/74	3.3	7	59	2.45	47	2000	67	2.58	40
5	60	120/77	3.1	14	85	1.73	83	1300	32	1.28	30
6	72	107/76	3.2	7	70	1.81	84	1300	37	1.48	25
Mean	74	126/78	3.0	12	71	1.88	64	1600	42	1.68	32
±SE	±6	±6/1	±0.2	±2	±4	±0.10	±6	±100	±2	±0.2	±4

BP = blood pressure (mm Hg); CI = cardiac index (liters/min per m^2); dp/dt = rate of change of pressure (mm Hg/sec); EF = ejection fraction (percent); FRCP = fractional rate of change of power at a ventricular pressure of 55 mm Hg (sec^{-1}); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEDVI = left ventricular end-diastolic volume index (ml/m^2); SE = standard error; V_{CF} = mean velocity of circumferential fiber shortening (sec^{-1}); Vmax = maximal velocity of contractile element shortening.

TABLE II

Hemodynamic Variables in Patients with Abnormal Ventricular Performance Based Upon Ejection Fraction, Mean Velocity of Circumferential Fiber Shortening and Left Ventricular End-Diastolic Volume Index

Case no.	HR	BP	CI	LVEDP	EF	V_{CF}	LVEDVI	Peak dp/dt (mm Hg/sec)	Maximal dp/dt / p	Vmax	FRCP
7	60	100/70	2.1	8	48	0.42	88	900	33	1.42	4
8	84	104/71	2.2	13	27	0.44	64	1300	35	1.57	20
9	83	92/65	2.1	12	27	0.64	53	1500	38	1.62	27
10	80	115/82	2.4	16	21	0.67	87	1200	25	1.36	27
11	76	105/74	3.0	12	36	0.67	108	900	23	1.03	16
12	64	91/61	2.2	14	44	0.56	74	800	25	1.12	5
13	73	110/70	2.4	10	46	0.88	108	1100	30	1.70	12
Mean	74	103/70	2.3	12	36	0.61	83	1100	30	1.40	16
±SE	±4	±3/3	±0.1	±1	±4	±0.06	±8	±100	±2	±0.1	±4
*P**	NS	<0.01/<0.05	<0.01	NS	†	†	NS	<0.02	<0.05	NS	<0.01

Abbreviations as in Table I.

* Probabilities (unpaired *t* test) refer to comparable hemodynamic data listed in Table I.

† The means of the ejection fraction and V_{CF} differed significantly ($P<0.001$) in patients with normal and abnormal venticular performance, but categories were defined on the basis of these indexes.

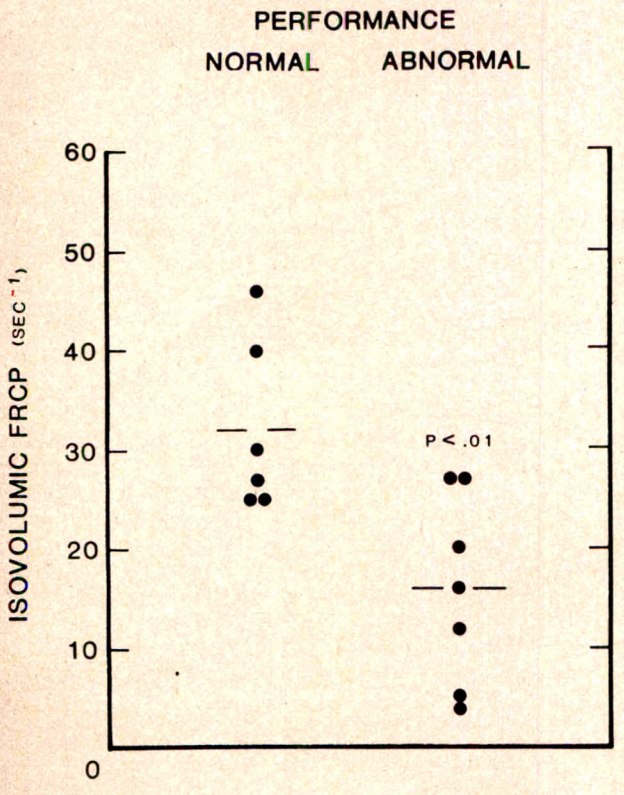
<0.02), there was a marked overlap of values (Tables I and II). Similarly, there was a wide overlap of values for maximal dp/dt/p. Vmax was comparable in patients with normal and reduced values for ejection fraction and velocity of circumferential fiber shortening (Tables I and II). Correlations of the fractional rate of change of power with maximal dp/dt/p and with Vmax were only approximate, the correlation coefficients being 0.51 and 0.50, respectively.

Discussion

The fractional rate of change of power was derived on the basis of physiologic and fluid dynamic principles, and it expresses a meaningful concept. The expression indicates that during states of higher contractility the ventricle can sustain a higher rate of change of power relative to instantaneous power. With states of augumented contractility, it was shown that the ventricle can sustain this higher ratio throughout nearly all of the isovolumic period.

Advantages: In contradistinction to the isovolumic rate of change of power, the fractional rate of change of power has the specific advantage of being calculable from an accurately recorded intraventricular pressure. Although end-diastolic volume and the isothermal modulus of volume elasticity are factors in the derivation of this expression, both cancel from the final equation for the fractional rate of change of power.

In dogs, the fractional rate of change of power reflected drug-induced alterations of the contractile state in a prominent fashion.[3] In the present study, it



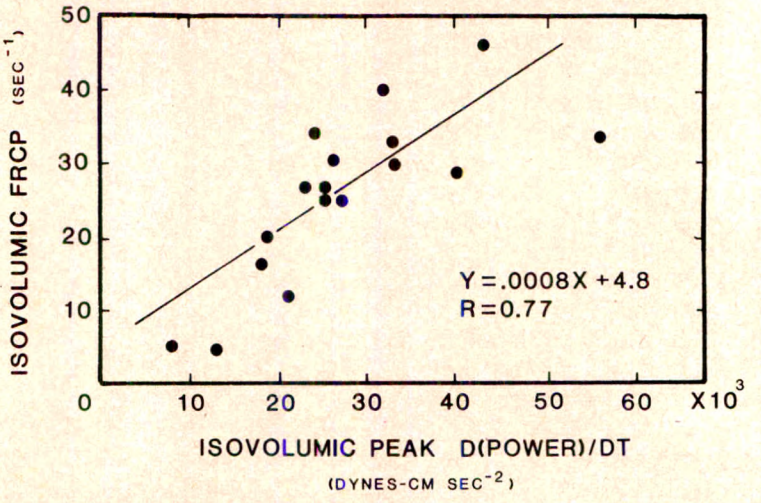


FIGURE 3 (left). Individual values for isovolumic fractional rate of change of power (FRCP) measured at a ventricular pressure of 55 mm Hg in patients with normal and abnormal ventricular performance. Values greater than 27 sec^{-1} were seen only in patients with normal performance.

FIGURE 4 (above). Isovolumic fractional rate of change of power (FRCP) shown as a function of isovolumic peak rate of change of power [d(power)/dt]. Correlation coefficient (r = 0.77) and a regression equation are shown.

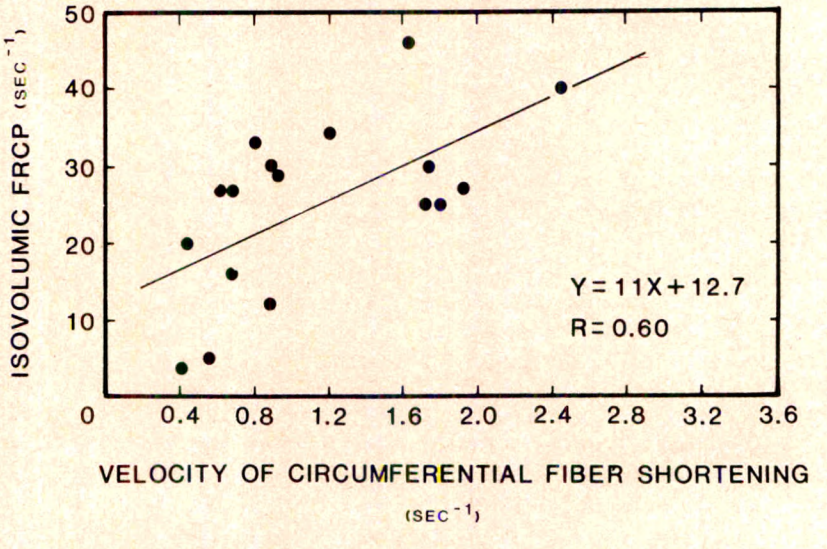


FIGURE 5. Isovolumic fractional rate of change of power (FRCP) shown as a function of the mean velocity of circumferential fiber shortening.

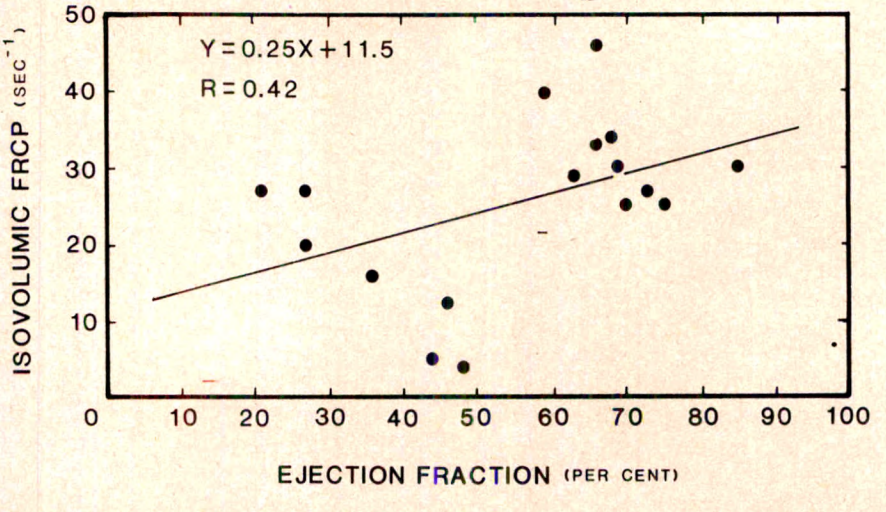


FIGURE 6. Isovolumic fractional rate of change of power (FRCP) shown relative to the ejection fraction.

permitted separation of patients with normal performance from those with reduced left ventricular performance. In a previous study[2] it was shown that use of peak isovolumic rate of change of power allowed distinction between patients with normal or reduced left ventricular performance and, in dogs, was also sensitive to drug-induced alterations of the contractile state, yet insensitive to changes of preload and afterload.[1]

Assumptions in derivation: The derivation of the fractional rate of change of power obviates problems concerning the application of theories of muscle mechanics to the determination of the contractile state of the intact heart.[6] The only assumption implicit in the derivation of the fractional rate of change of power is that of isothermal conditions during the isovolumic period.[1] The validity of this assumption has been previously discussed. No assumptions are made in regard to the synergy of isovolumic contraction, uniformity of muscle fiber orientation, ventricular geometry, the elasticity of muscle fibers or an un changing shape of the ventricle during isovolumic contraction. Other considerations in the derivation of isovolumic energy, power and the rate of change of power also apply to the isovolumic fractional rate of change of power.[1,2] A nonregurgitant atrioventricular valve is implied.

Physiologic relations: A component of the fractional rate of change of power previously shown by others[5,7] to be a useful index of performance, 1/p dp/dt, now may be recognized as having a physiologic meaning based upon the fractional rate of change of power. At peak dp/dt, the second term of the fractional rate of change of power (1/ṗ dṗ/dt) becomes zero. Therefore, it can be shown that 1/p dp/dt at peak dp/dt is the same as the fractional rate of change of power at peak dp/dt.

The isovolumic fractional rate of change of power, in an uncomplicated fashion, relates indexes of ventricular performance derived on the basis of fluid dynamics (power, rate of change of power, dp/dt) to indexes of performance based upon theories of muscle mechanics. Contractility of the intact heart[8,9] as well as isolated cardiac muscle[10] has been characterized by the instantaneous relations between myocardial force, velocity and fiber length. The isovolumic fractional rate of change of power readily can be expressed in terms of the velocity of contractile element shortening (V_{CE}), and the rate and acceleration of force (tension) along the ventricular wall provided that certain assumptions are made (Appendix). This relation is as follows:

$$FRCP = KV_{CE} + \left(\frac{d^2T}{dt^2}\right)\left(\frac{dT}{dt}\right)^{-1}$$

where dT/dt and d^2T/dt^2 are the rate of change and acceleration of wall tension, respectively, and K is the elastic modulus of cardiac muscle. Seemingly diverse characteristics of performance (energy, power, rate of change of power, dp/dt, V_{CE} and rate of change of wall tension) are thereby shown to be interrelated through the expression indicative of the fractional rate of change of power.

In summary, the fractional rate of change of ventricular power during isovolumic contraction represents the instantaneous rate of change of power developed by the ventricle relative to instantaneous power. It was derived on the basis of rates and accelerations of energy transfer during the isovolumic period. Its derivation is based upon established principles of fluid dynamics. No assumptions related to ventricular geometry, uniformity of contraction, fiber orientation or elasticity of muscle fibers are implicit in the expression. The isovolumic fractional rate of change of power, in the present study, permitted distinction between patients with normal and abnormal ventricular performance. The fractional rate of change of power, in an uncomplicated fashion, relates characteristics of performance derived on the basis of fluid dynamics to indexes of performance derived on the basis of muscle mechanics. Although the isovolumic rate of change of power, from which the fractional rate of change of power was derived, has many of the attributes of the fractional rate of change of power, the latter has the specific advantage of being calculable from a carefully measured intraventricular pressure.

Appendix

The isovolumic fractional rate of change of ventricular power can be expressed in terms of tension along the ventricular wall and velocity of contractile element shortening (V_{CE}) as will be shown in the following derivations:

The isovolumic fractional rate of change of power, as written in Equation 3 of the text, is:

$$FRCP = \frac{1}{p}\frac{dp}{dt} + \frac{1}{\dot{p}}\frac{d\dot{p}}{dt} \qquad (1A)$$

where p = intraventricular pressure (dynes cm^{-2}), dp/dt = ṗ = rate of change of intraventricular pressure (dynes cm^{-2} sec^{-1}) and dṗ/dt = the acceleration of intraventricular pressure (dynes cm^{-2} sec^{-2}).

It has previously been shown by others[4] that the velocity of contractile element shortening during isovolumeric contraction can be approximated as:

$$V_{CE} = \frac{1}{K}\frac{1}{p}\frac{dp}{dt} \qquad (2A)$$

where K is the elastic modulus of cardiac muscle.

Several assumptions are implicit in Equation 2A, and these have been described in detail.[6] Any uncomplicated configuration of ventricular geometry can be assumed. For simplicity of calculation, assume that the ventricle has a spherical configuration, with a thin wall.

According to the Laplace equation:

$$p = 2hT/r$$

where T = tension (dynes cm^{-1}), p = pressure (dynes cm^{-2}), r = radius (cm) and h = wall thickness (cm).

Assume the radius and wall thickness are constant during the isovolumic period. Thus, by differentiating the Laplace equation:

$$\dot{p} = \frac{2h}{r}\frac{dT}{dt} \qquad (4A)$$

Differentiating equation 4A:

$$\frac{d\dot{p}}{dt} = \frac{2h}{r}\frac{d^2T}{dT^2} \qquad (5A)$$

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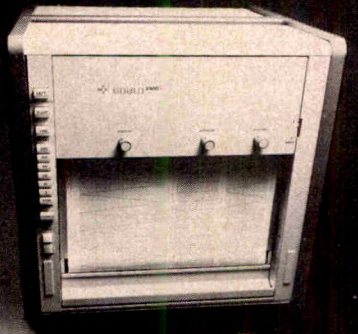

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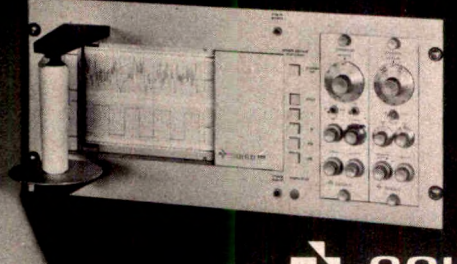

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Sublingual or Oral Tablets

* **INDICATIONS**

Based on a review of a related drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Sublingual "Probably" effective:
For the treatment of acute anginal attack and for prophylaxis in situations likely to provoke such attacks.

Oral "Possibly" effective:
For the relief of angina pectoris. It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Idiosyncrasy to this drug.

WARNINGS:
Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS:
Intraocular pressure is increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

ADVERSE REACTIONS:
Cutaneous vasodilation with flushing.
Headache is common and may be severe and persistent.
Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
On occasion an individual may exhibit marked sensitivity to the hypotensive effects of nitrate, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Please see package insert for full prescribing information.

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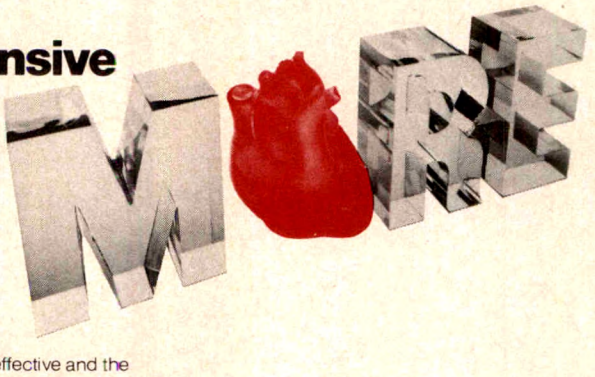


*The oral form of this drug has been evaluated as "possibly" effective and the sublingual form as "probably" effective for this indication. Please see brief summary on opposite page.

COS-122/150-5

A51

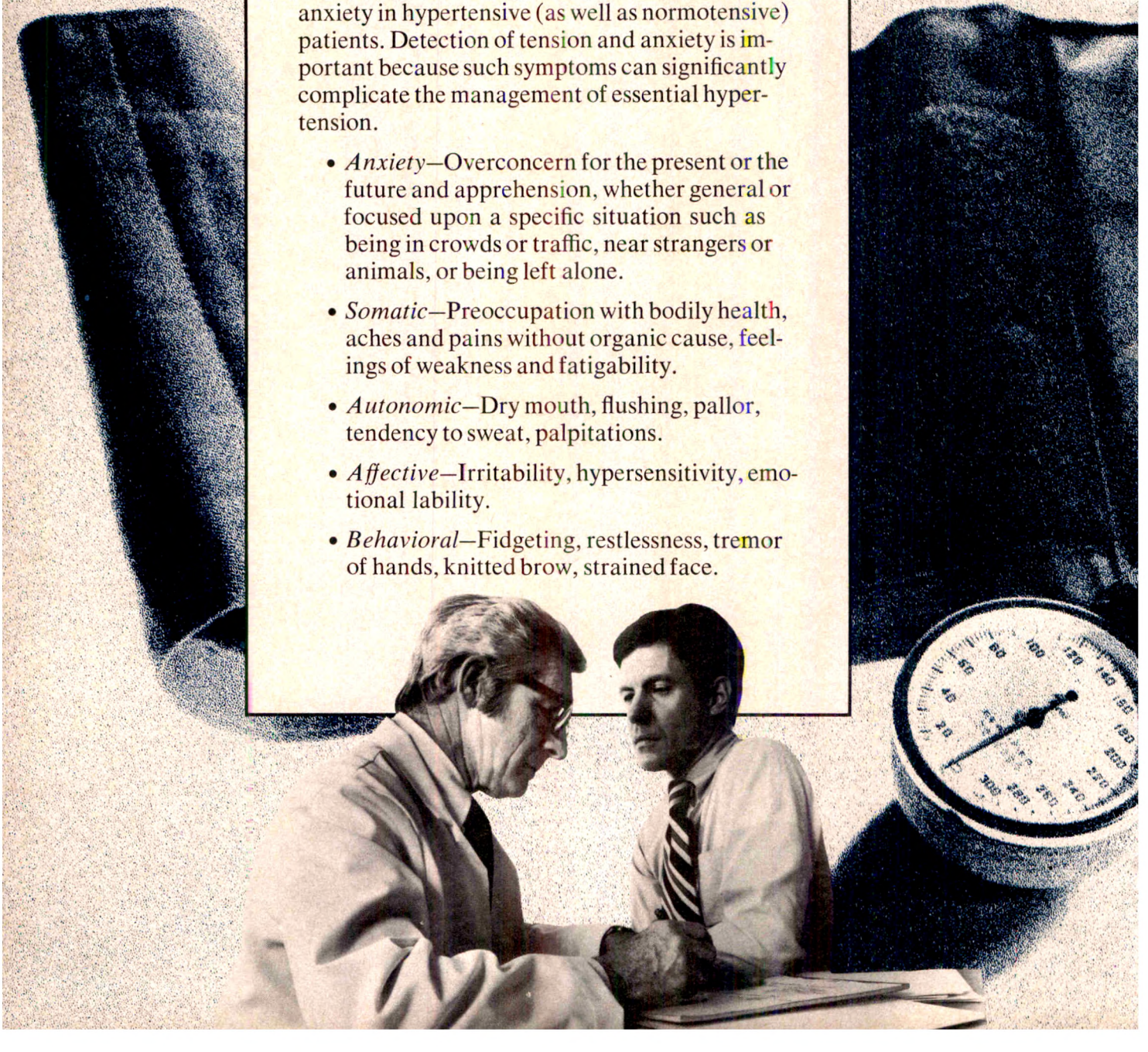
An important aspect of hypertension management.

Detection of

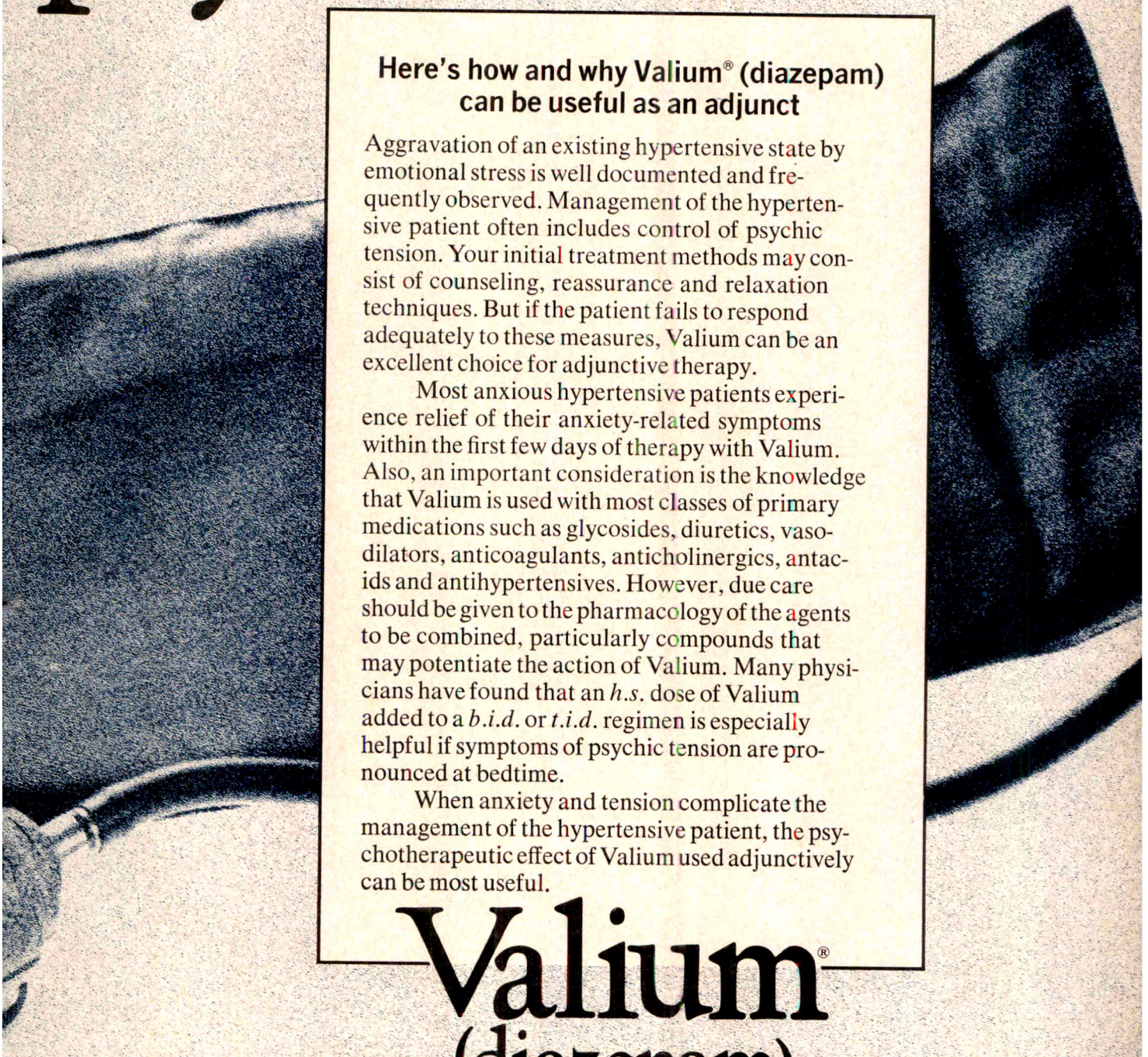
Here's how excessive psychic tension may express itself in the hypertensive patient

The following signs and symptoms—taken from a number of widely used psychiatric rating scales—may be useful in diagnosing psychic tension and anxiety in hypertensive (as well as normotensive) patients. Detection of tension and anxiety is important because such symptoms can significantly complicate the management of essential hypertension.

- *Anxiety*—Overconcern for the present or the future and apprehension, whether general or focused upon a specific situation such as being in crowds or traffic, near strangers or animals, or being left alone.
- *Somatic*—Preoccupation with bodily health, aches and pains without organic cause, feelings of weakness and fatigability.
- *Autonomic*—Dry mouth, flushing, pallor, tendency to sweat, palpitations.
- *Affective*—Irritability, hypersensitivity, emotional lability.
- *Behavioral*—Fidgeting, restlessness, tremor of hands, knitted brow, strained face.



psychic tension



Here's how and why Valium® (diazepam) can be useful as an adjunct

Aggravation of an existing hypertensive state by emotional stress is well documented and frequently observed. Management of the hypertensive patient often includes control of psychic tension. Your initial treatment methods may consist of counseling, reassurance and relaxation techniques. But if the patient fails to respond adequately to these measures, Valium can be an excellent choice for adjunctive therapy.

Most anxious hypertensive patients experience relief of their anxiety-related symptoms within the first few days of therapy with Valium. Also, an important consideration is the knowledge that Valium is used with most classes of primary medications such as glycosides, diuretics, vasodilators, anticoagulants, anticholinergics, antacids and antihypertensives. However, due care should be given to the pharmacology of the agents to be combined, particularly compounds that may potentiate the action of Valium. Many physicians have found that an *h.s.* dose of Valium added to a *b.i.d.* or *t.i.d.* regimen is especially helpful if symptoms of psychic tension are pronounced at bedtime.

When anxiety and tension complicate the management of the hypertensive patient, the psychotherapeutic effect of Valium used adjunctively can be most useful.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg tablets

adjunct for the overly tense hypertensive patient

ROCHE

Please see following page for a summary of product information.

adjunct for the overly tense hypertensive patient

Valium®
(diazepam)
2-mg, 5-mg, 10-mg tablets

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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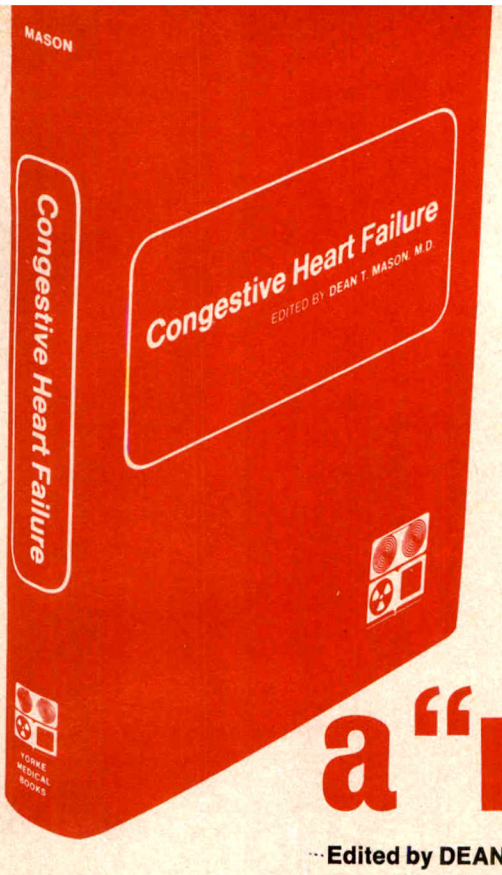

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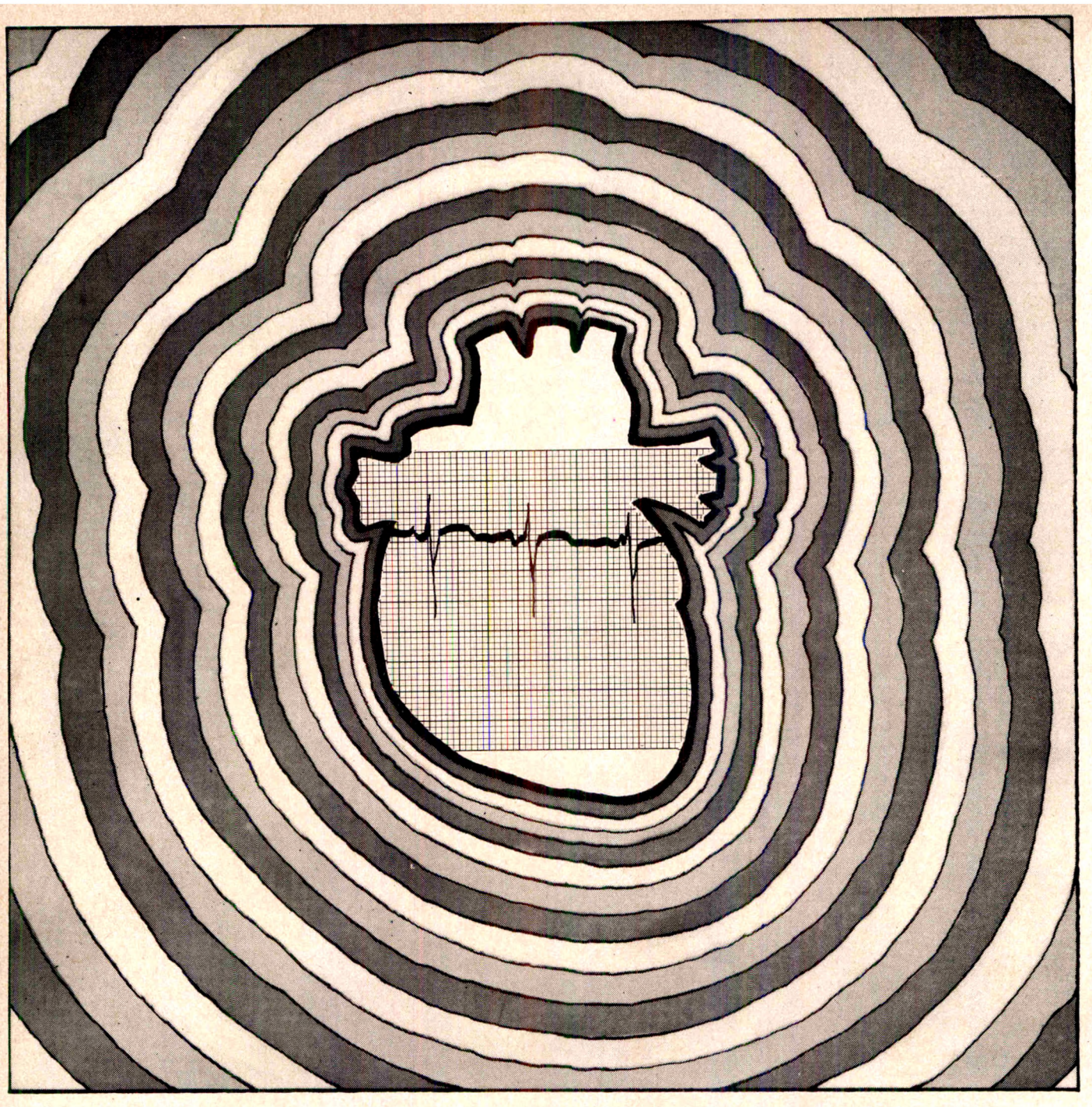

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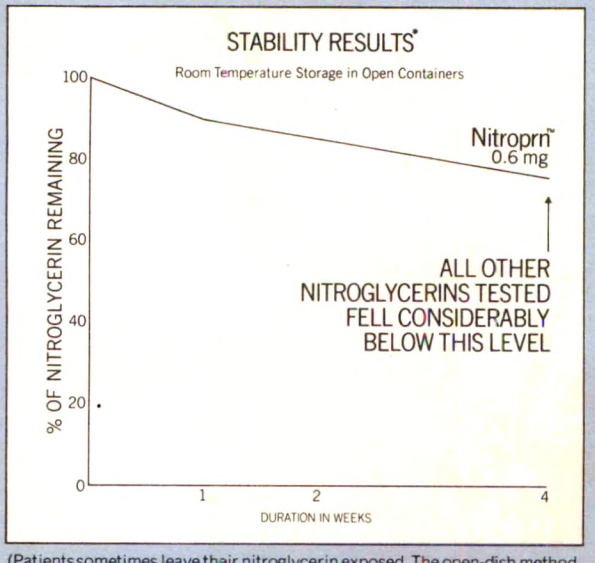

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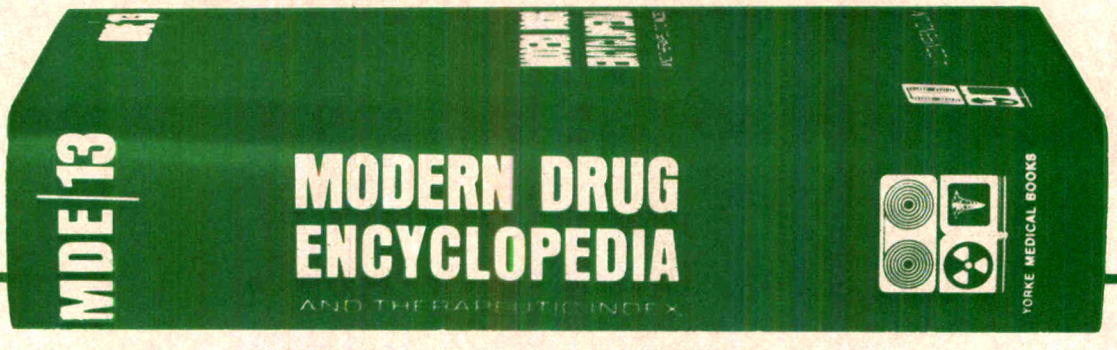

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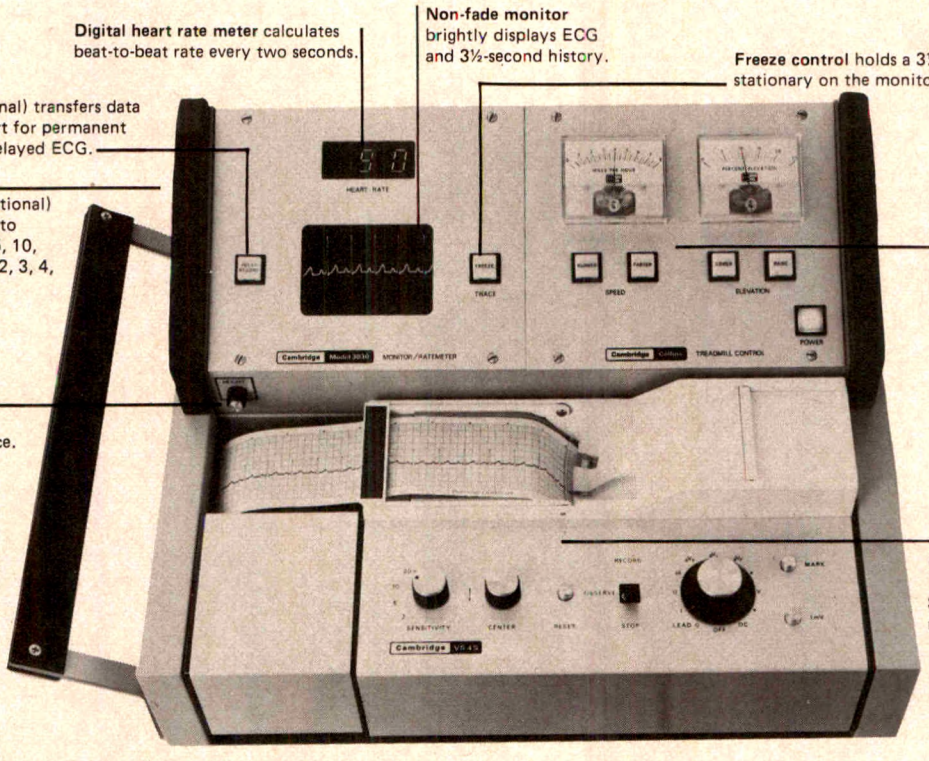

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(See prescribing information on next page.)

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

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INDICATIONS: Hypertension: DIUCARDIN alone may provide adequate control in mild or moderate hypertension. In severe hypertension or in cases of mild or moderate hypertension which do not respond adequately, DIUCARDIN may be used in conjunction with other antihypertensive agents.

DIUCARDIN alone or in conjunction with other antihypertensive agents is indicated for control of hypertension in pregnancy. (See WARNINGS)

Edema: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: Usual adult dosage: 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN —No. 702—Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.

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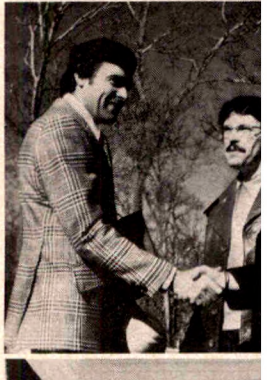

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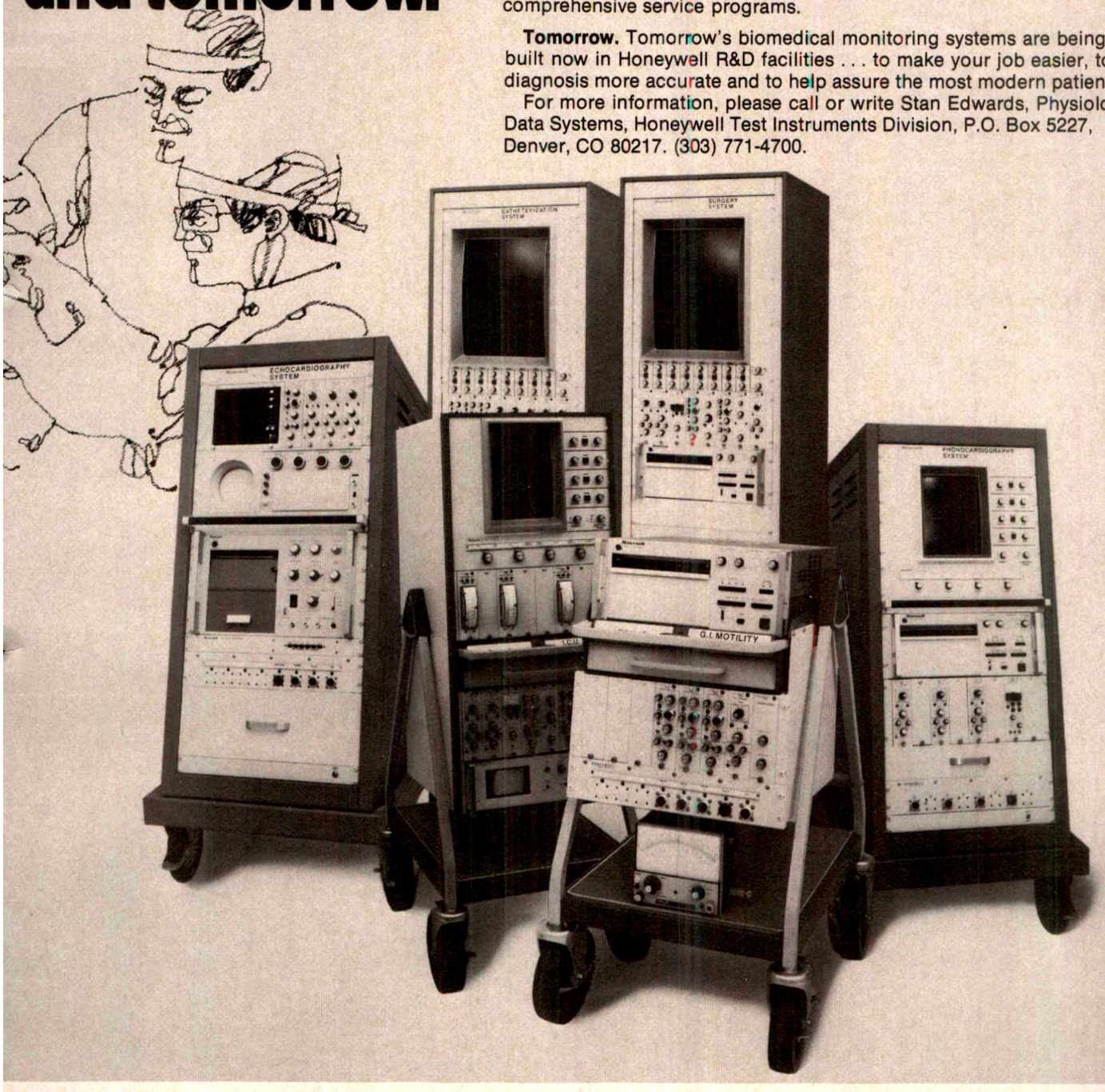

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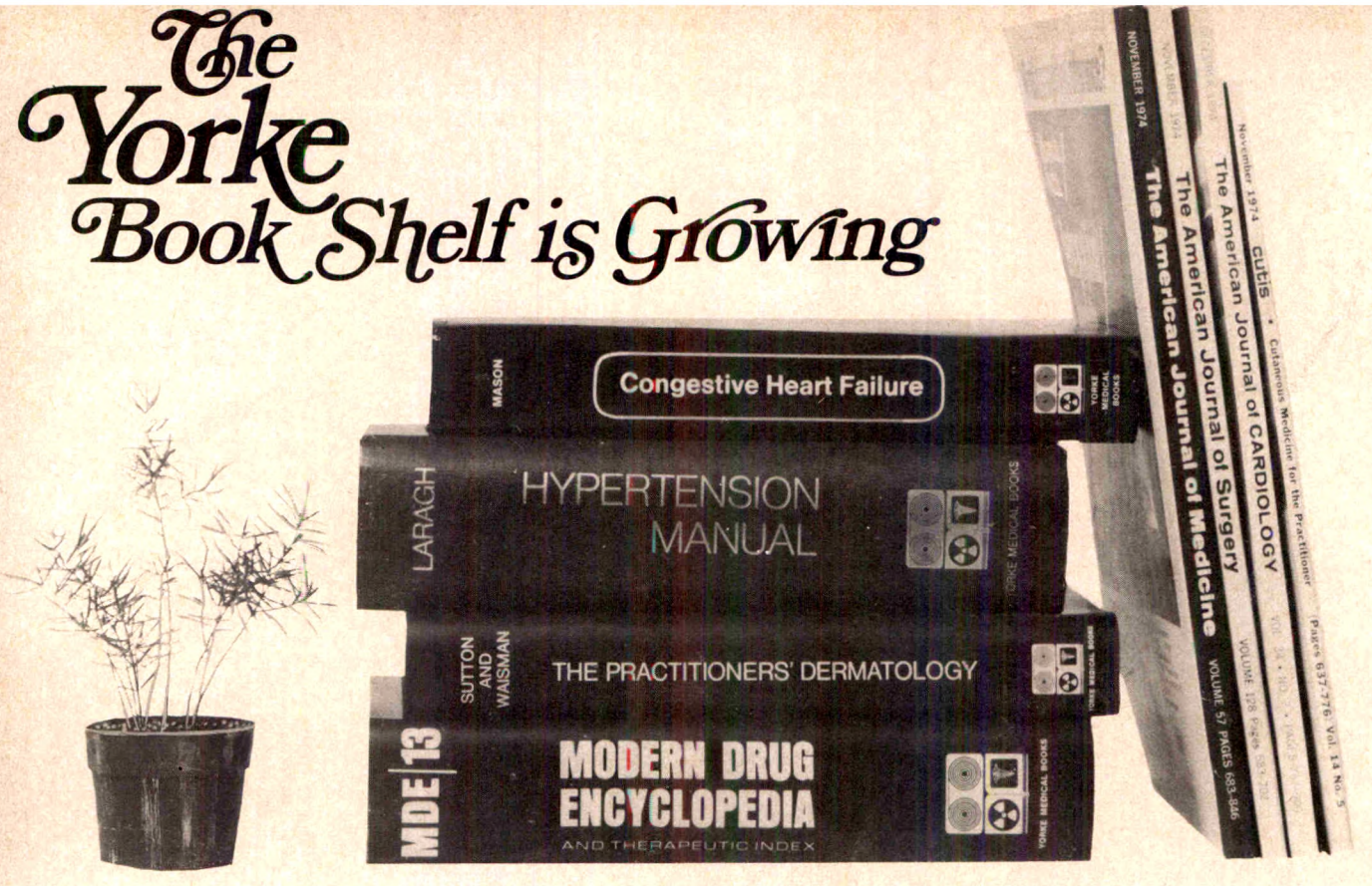

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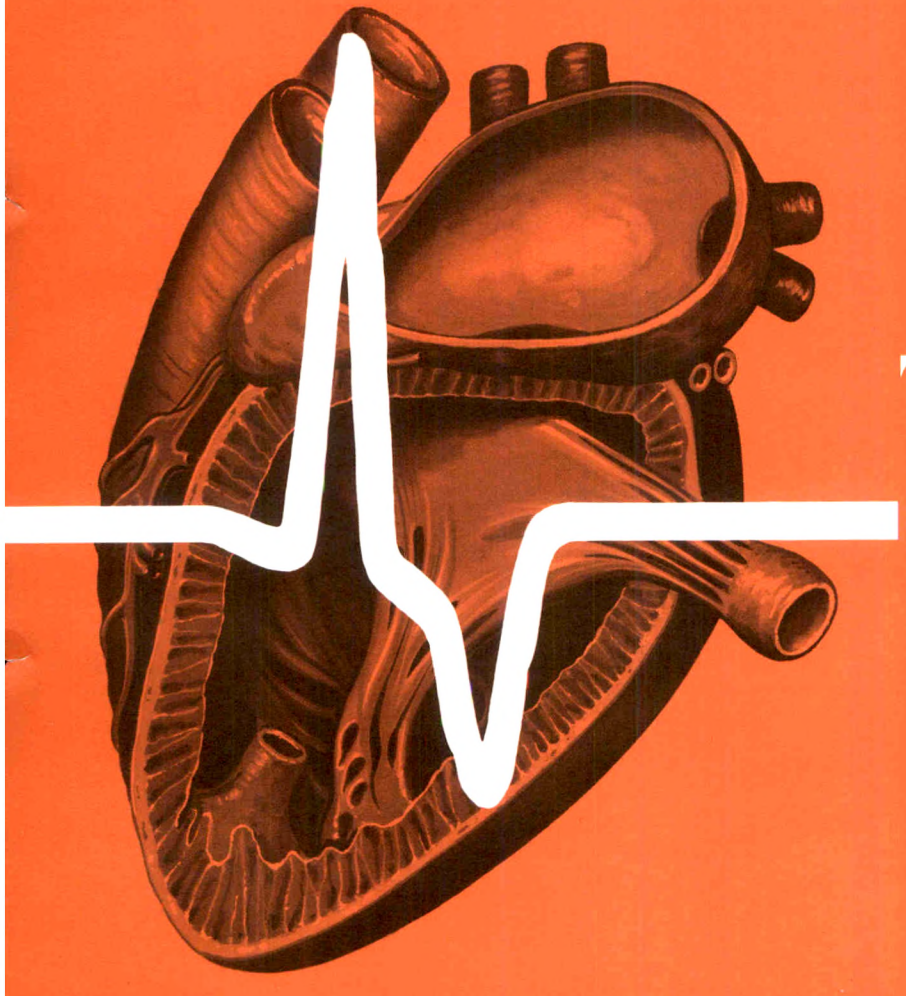

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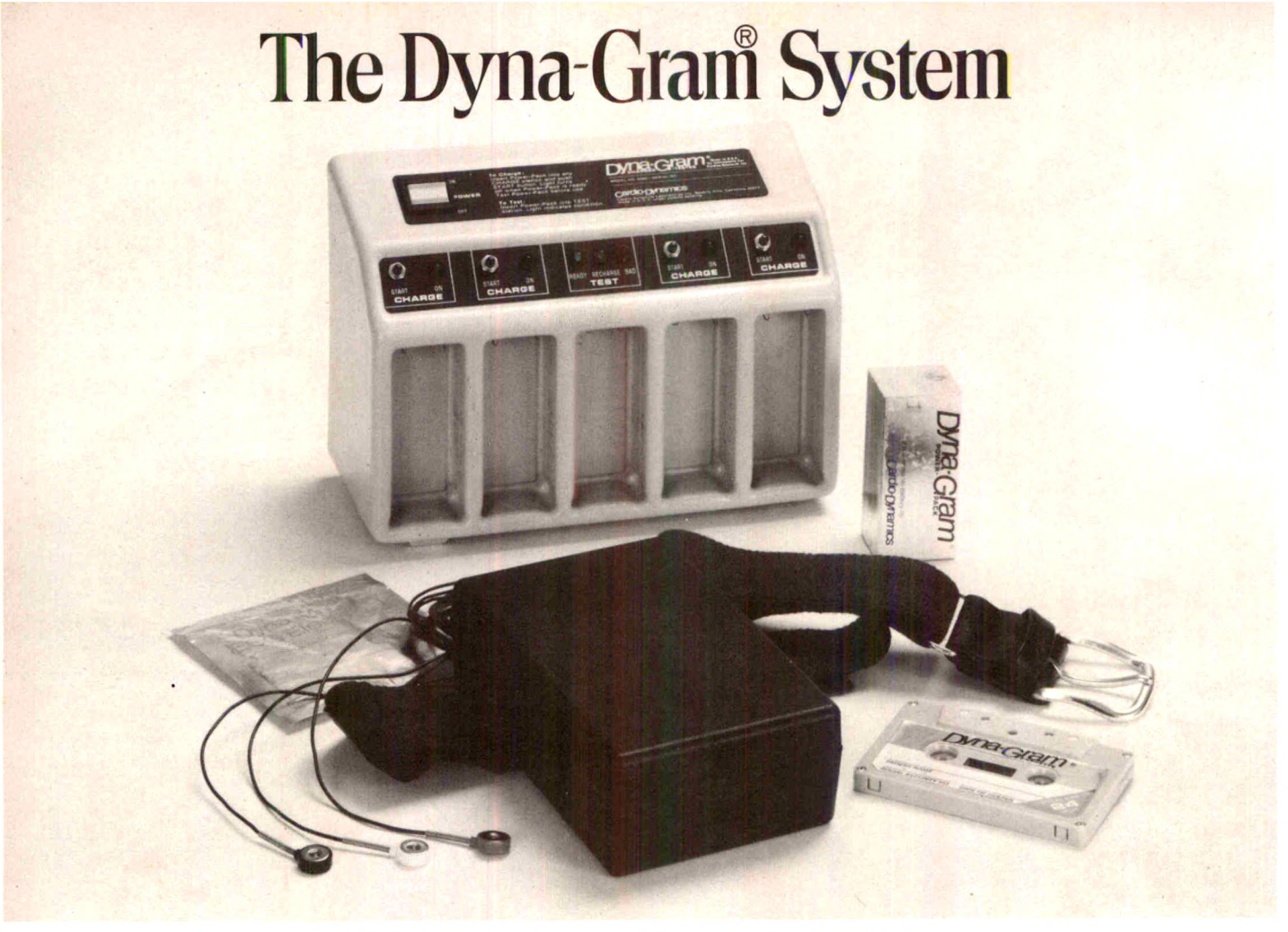

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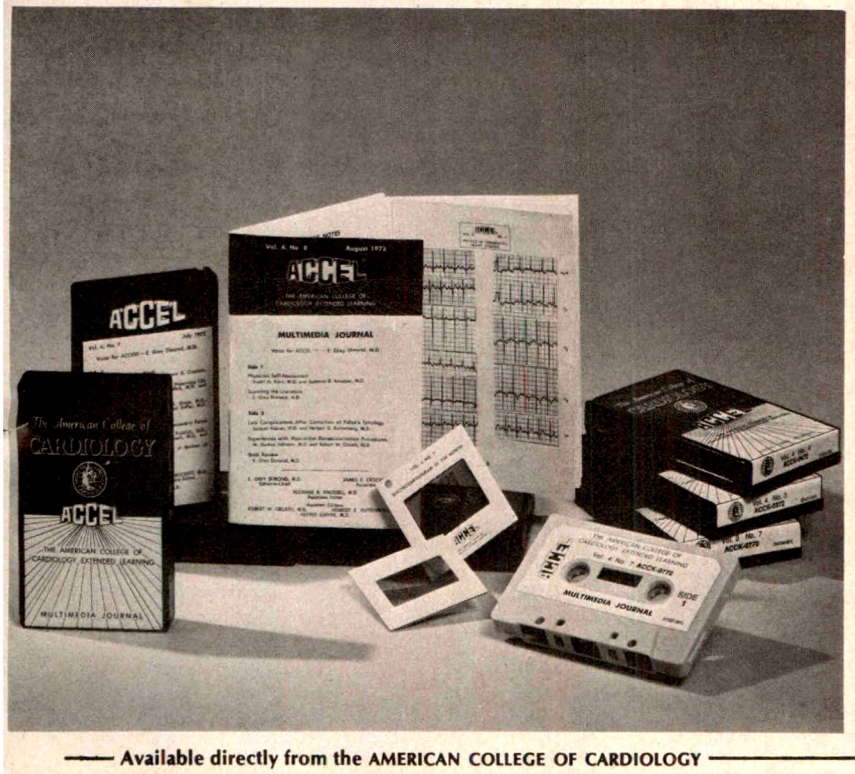

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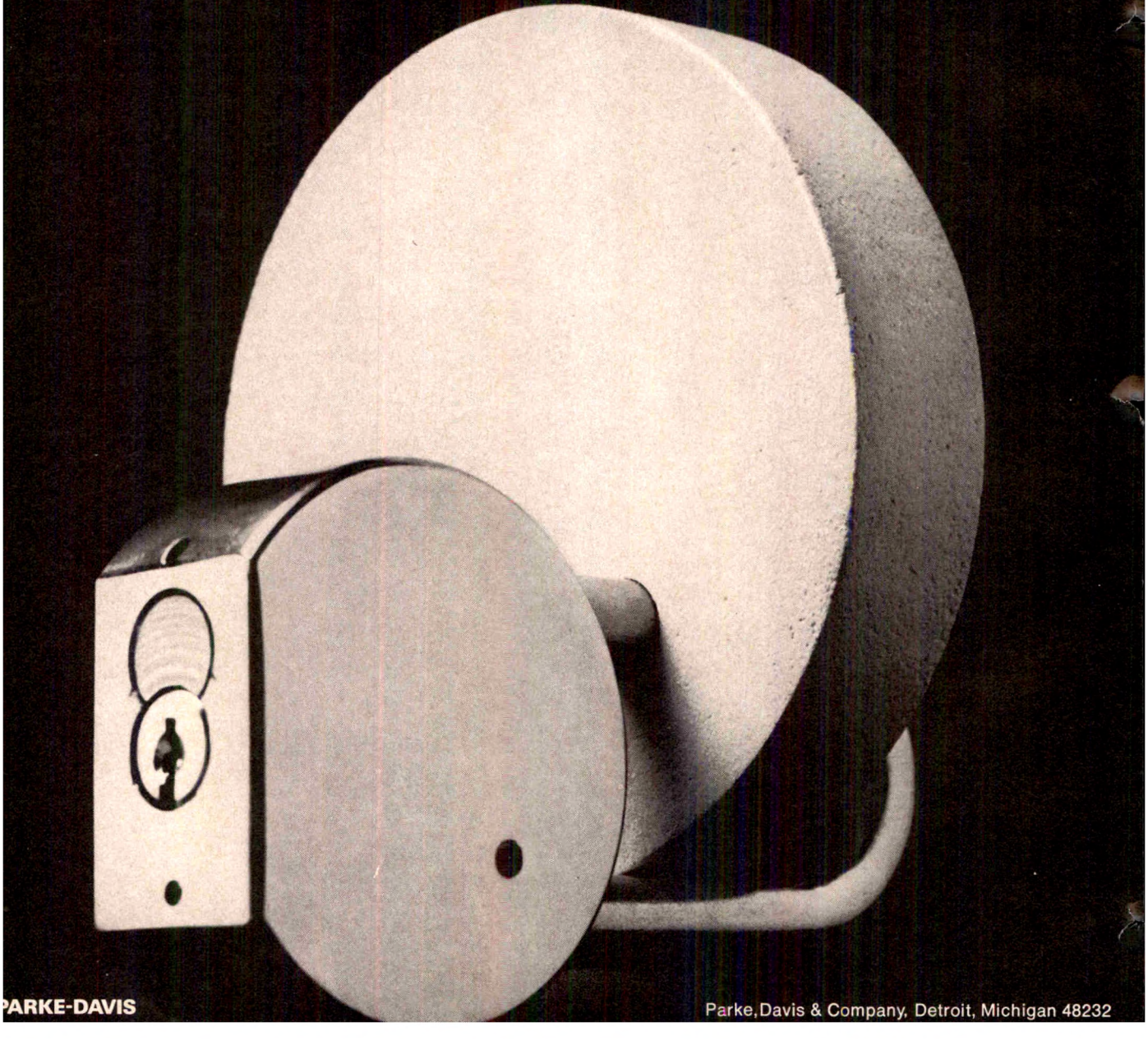

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Solitary Interruption of the Arch of the Aorta

Clinicopathologic Review of Eight Cases

M. RENATE DISCHE, MD
MARY TSAI, MD
HAROLD A. BALTAXE, MD

New York, New York

Patients with isolated total interruption of the arch of the aorta not accompanied by other cardiovascular anomalies may survive to advanced age. Their symptoms and course resemble those of patients with postductal coarctation of the aorta. However, there are basic differences in the pathologic findings in these two types of anomalies that may be of aid in the radiographic diagnosis.

Interruption and complete atresia of the arch of the aorta has been reported in about 250 patients.[1–22] Although once thought to be a rare anomaly recognized only at necropsy, it is now diagnosed during life and is amenable to surgical repair.[2,15] Usually, the anomaly is not isolated but is accompanied by a persistent patent ductus arteriosus and intracardiac shunts, particularly ventricular septal defects.[23] The survival time of patients with such compound anomalies is generally short.

Among 250 patients with interruption or atresia of the arch 6 patients were described whose interruption was a solitary lesion not accompanied by supra- or intracardiac shunts. We[7] recently added two more who, within a year, had their condition diagnosed angiographically and underwent successful surgical repair at The New York Hospital.[7] We present here a brief review of the clinicopathologic findings in these eight cases. Patients with solitary interruption form a distinct group by virtue of the clinical course, pattern of the anomaly and ensuing complications.

Results

Clinical Findings

Longevity: The most striking feature common to this group of patients is the relatively benign course of the disease and the longevity of those affected by it (Table I). The age range at the time of diagnosis ranged from 8 to 56 years (average age 28 years). The only recorded fatality[24] occurred in a 32 year old man who died from acute bacterial endocarditis in the era before antibiotic therapy and operative repair. The remaining seven patients were all reported to be alive and well after corrective surgery.

Symptoms: In spite of various symptoms most of these patients were able to lead active lives, some engaging in strenuous activities.[8,10] However, only one patient remained entirely asymptomatic throughout his life.[8] Three patients experienced easy fatigability, dyspnea, headaches and palpitations on exertion[13,14,25] Two patients had progressive intermittent claudication and paresthesia in the legs,[8,25] and some had epistaxis and profuse sweating of the head. Transient cerebral symptoms, such as visual blurring and aphasia, were the presenting complaints in one of our two patients.[7]

Physical findings (Table I): The pulses in the neck were strong and bounding in seven patients whose clinical history was available;

From the Departments of Pathology, Pediatric Cardiology and Radiology, The New York Hospital-Cornell University Medical Center, New York, N.Y. This study was partially supported by Grant 1 TO 1 HL05966-02 CAR from the National Institute of Health, Bethesda, Md. Manuscript accepted May 30, 1974.

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TABLE I

Atresia and Interruption of the Arch of the Aorta: Clinical Data

Case no.	Author	Age (yr) & Sex	Type	Vessels from Descending Aorta	Pulsations						Blood Pressure (mm Hg)			
					Neck		Radial		Femoral		Arms		Legs	
					R	L	R	L	R	L	R	L	R	L
1	Evans[24] (Case 19)	32M	A*	...	...	...	...	...	...	...	...	...	...	...
2	Kauff et al.[7] (Case 1)	36M	A	...	4+	4+	4+	2+	1+	1+	180/120	140/110	0	0
3	Kauff et al.[7] (Case 2)	49M	A_2	RSCA	4+	4+	2+	4+	0	0	120/90	210/95	0	0
4	LePage et al.[8]	56M	A*	...	4+	4+	4+	4+	2+	2+	184/100	174/100	140/100	140/100
5	Zetterqvist[13]	8M	B_2	RSCA LSCA	0	4+	0	0	0	0	0	0	0	0
6	Asano et al.[14]	12F	B	LSCA	4+	4+	4+	1+	0	0	210/70	120/60	90/70	90/70
7	Morgan et al.[10]	19M	B_2	RSCA LSCA	4+	4+	0	0	0	0	95/70	95/70	95/70	95/70
8	Pillsbury et al.[25]	16F	C	LCA LSCA	4+	0	4+	0	1+	1+	148/100	0	0	0

* Cases of atresia.

L = left; LCA = left carotid artery; LSCA = left subclavian artery; R = right; RCA = right carotid artery; RSCA = right subclavian artery.

this condition was bilateral in five but unilateral in two patients.[13,25] Hypertension in the arms, either bilateral or unilateral, was documented in five patients. Two of the older patients exhibited papilledema and hypertensive retinopathy.[7] The peripheral pulses in the legs were weaker than the weakest pulse in the arms in all four cases in which this was mentioned. The character of the pulses in the arms depended entirely on the site of origin of the subclavian vessel from the aorta: If the vessel originated from the ascending aorta proximal to the interruption, strong pulsations were transmitted; if it arose from the descending aorta distal to the interruption the arterial pulsations were always feeble (Table I). Cyanosis and clubbing of the digits were not mentioned.

Cardiac murmurs were present in all but one patient.[8] The duration of these murmurs was not certain, but in two patients[13,25] no murmur was noted at birth and in another a murmur was first heard when the patient was 24 years old.[7] These murmurs were usually grade 2–4/6 in intensity, systolic ejection in type and often were best heard in the second right or left intercostal space and transmitted to the interscapular region, the neck and even over the entire head[13] where they were best detected just behind the ears. A murmur of aortic stenosis was noted in one patient[7] in whom a bicuspid aortic valve with extensive arteriosclerotic change of the ascending aorta was suspected.

Radiologic findings: Chest roentgenograms generally indicated enlargement of the left atrium and ventricle. Particularly in older patients, there was dilatation of the ascending aorta. The aortic knob was frequently not visible and the descending aorta was poorly defined. In cases in which the right subclavian artery took its origin from the descending aorta, an indentation of the posterior esophagus could be seen. Rib notching was a common finding. The pulmonary circulation was generally normal.

The correct diagnosis was made after ascending and descending aortography in the seven patients who survived.

Surgical Repair

Seven of eight patients were successfully operated upon, three by direct anastomoses[7,8,13] and four by interposition of a graft between the proximal and distal aortic stumps. All patients survived the operative procedure. Claudication and paresthesia reportedly completely disappeared but hypertension persisted although it was less severe.

Anatomic Findings

The site of interruption of the arch of the aorta and location of its branches were well studied in all eight cases, in one during postmortem examination[24] and in the remaining seven by angiography and during surgical repair (Table II).

Site of the interruption: According to Celoria and Patten[26] interruptions of the arch of the aorta are subdivided into three main categories depending on the site of interruption (Fig. 1). In the about equally common types A and B, the interruption lies distal (A) or just proximal (B) to the origin of the left subclavian artery (Fig. 1, A and C). In the rare third (C) type the interruption is located between the two common carotid trunks (Fig. 1E). Further variation in the clinical and pathologic findings is introduced by the variable origin of the right subclavian artery, which frequently arises from the descending aortic

TABLE II

Atresia and Interruption of the Arch of the Aorta: Pathologic Findings

Case no.	Type		Cardiac Enlargement	Aortic Valve	Aorta		Ductus Ligament	Stenosis of LSCA
					Ascending	Descending		
1	A		+	Bicuspid; endocarditis	Dilated; atheromatous	...	Not identified	–
2	A		+	Bicuspid; calcified	Dilated; arterio-sclerotic	Small	+	+
3	A_2		+	...	...	...	+	...
4	A		...	Normal	...	...	...	...
5	B_2		+	Normal	Dilated; blind RCA	Small	+	+
6	B		+	...	Dilated	Small	...	...
7	B_2		–	...	Normal	Small	+	...
8	C		–	Normal	Normal	Small	+	...

– = absent; + = present; LSCA = left subclavian artery; RCA = right carotid artery.

segment distal to the interruption. It may be the only major vessel taking its origin from the distal stump, as in type A_2 interruption (Fig. 1B), or it may arise from the distal stump together with the left subclavian artery, as in type B_2 interruption (Fig. 1D). The descending aortic origin of the right subclavian artery in type C_2 interruption (Fig. 1F) has not been described. In the eight cases reviewed here, four had type A, three had type B and one had type C interruption (Table II). The right subclavian artery arose from the descending aorta in three cases, indicating an unusually high prevalence rate of this associated malformation.

In two of the eight cases a short fibrous band connected the proximal and distal segments of the aorta; in the remaining six cases there was no connection between the stumps. The size of this gap is of importance in surgical correction, as is the diameter of the blind proximal and distal aortic stumps. In three of the seven patients who underwent operative repair, the blind ends of the aorta were closely apposed[7,8,13]; in the remaining four a variable gap existed.

Bicuspid aortic valves: Such valves are frequently associated with aortic arch anomalies. Two of the eight patients had a bicuspid aortic valve.[7*,24]

Ductus arteriosus: Absence of a patent ductus arteriosus characterizes isolated interruption of the

* Case 1.

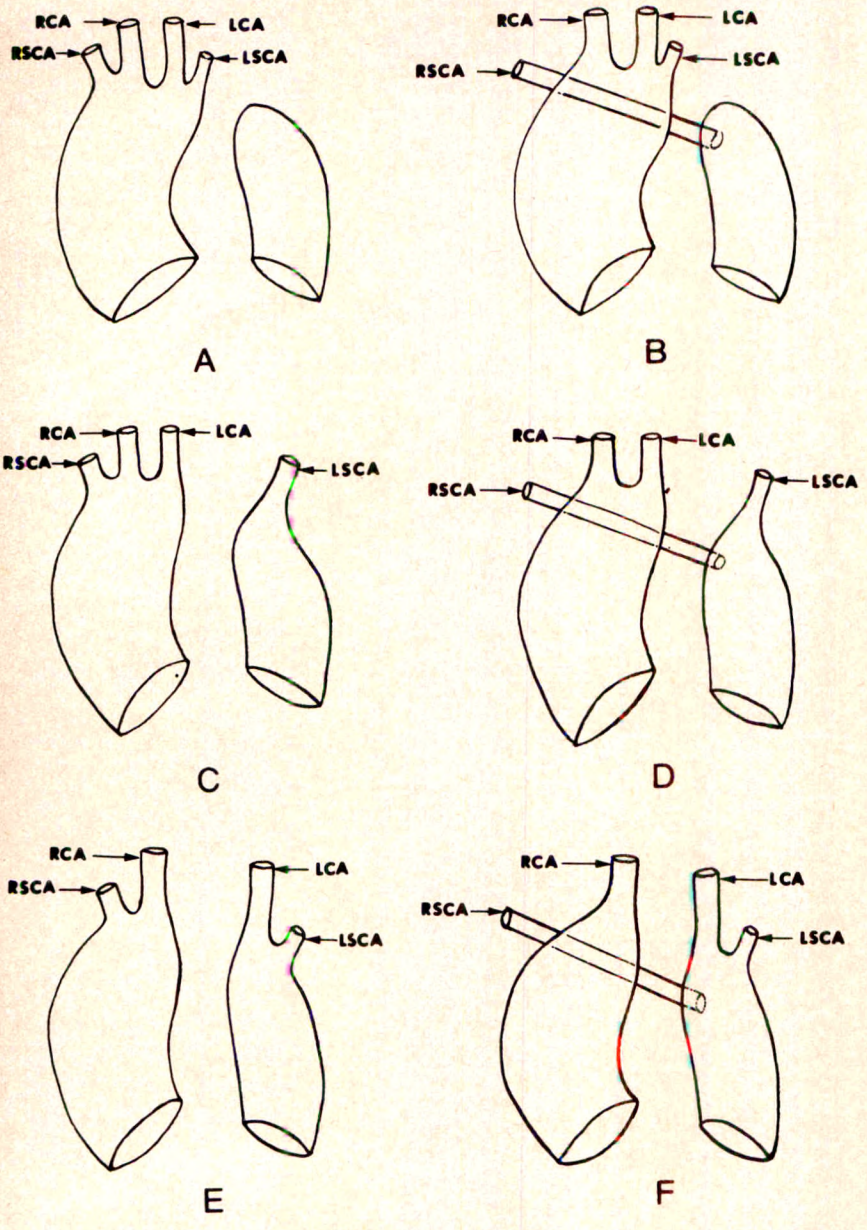

FIGURE 1. Types of interruption of the arch of the aorta according to Celoria and Patten.[26] **A,** type A: interruption distal to the left subclavian artery. **B,** type A_2: interruption distal to the left subclavian artery; origin of the right subclavian artery from the descending aorta. **C,** type B: interruption between the left common carotid artery and the left subclavian artery. The left subclavian artery arises from the descending aorta. **D,** type B_2: interruption between the left common carotid artery and the left subclavian artery. Both right and left subclavian arteries arise from the descending aorta. **E,** type C: interruption between the right and left common carotid arteries. The left subclavian artery arises from the descending aorta. **F,** type C_2: interruption between the right and left common carotid arteries. The right and left subclavian arteries arise from the descending aorta. This variant of interruption has not been observed so far. LCA = left carotid artery; LSCA = left subclavian artery; RCA = right carotid artery; RSCA = right subclavian artery.

arch of the aorta. However, in five of the eight cases a definite ligamentum arteriosum was identified at surgery. This structure connected the pulmonary artery to the descending aortic limb (four cases)[7,10,13] and to the ascending limb (one case).[25] The presence or absence of a ductus ligament was not mentioned in two and not identified in one case.

Stenosis of the left subclavian artery: Stenosis of the left subclavian artery at its point of origin from the aorta was present in two of the eight patients[7*,13] and was readily identified by angiography (Fig. 2 to 4).

Hypertensive angiopathy: Not unexpectedly there was anatomic evidence of hypertension in the ascending aortic limb and its branches with widening of the lumen of the aorta, tortuosity of the branches and accelerated arteriosclerotic changes in their walls. The descending aorta was smaller than the dilated ascending limb, but the differences in size and thickness of the walls did not lead to difficulties during surgical repair.

Collateral supply: Extensive collateral circulation was present in seven of the eight patients and appeared to become more prominent with advancing age. In addition, a "vertebral steal" phenomenon was noted when the subclavian artery arose from the descending aorta. In the youngest patient[13] this appeared to be the only route of blood to the distal aortic limb. Occasionally collateral vessels were large enough to compress the spinal cord.[8]

Discussion

Interruption of the arch of the aorta has long been considered a rare and highly fatal cardiovascular

* Case 1.

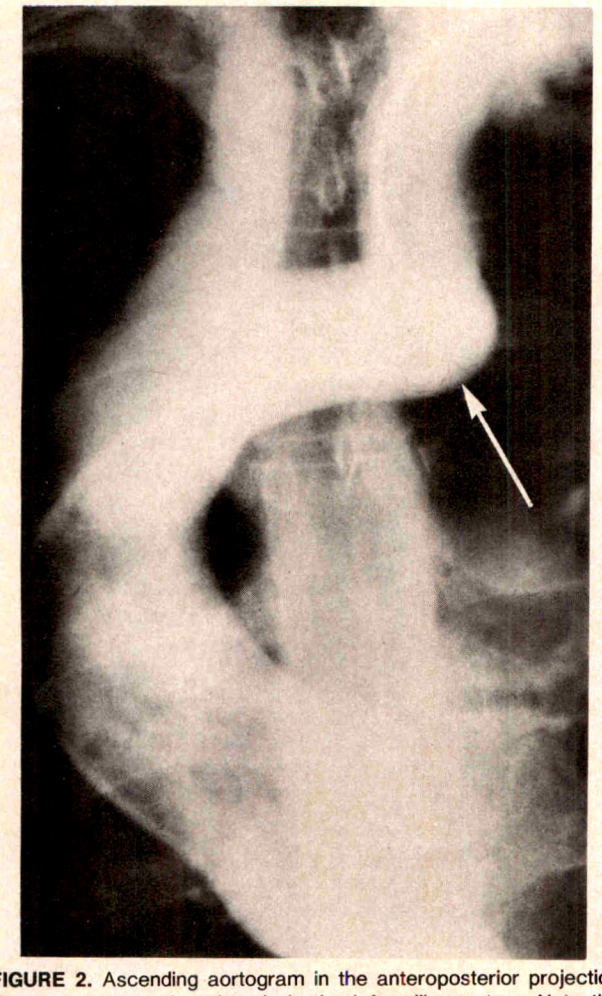

FIGURE 2. Ascending aortogram in the anteroposterior projection. The catheter was introduced via the left axillary artery. Note that there is lack of opacification of the distal aorta. The arrow points to the interruption of the arch.

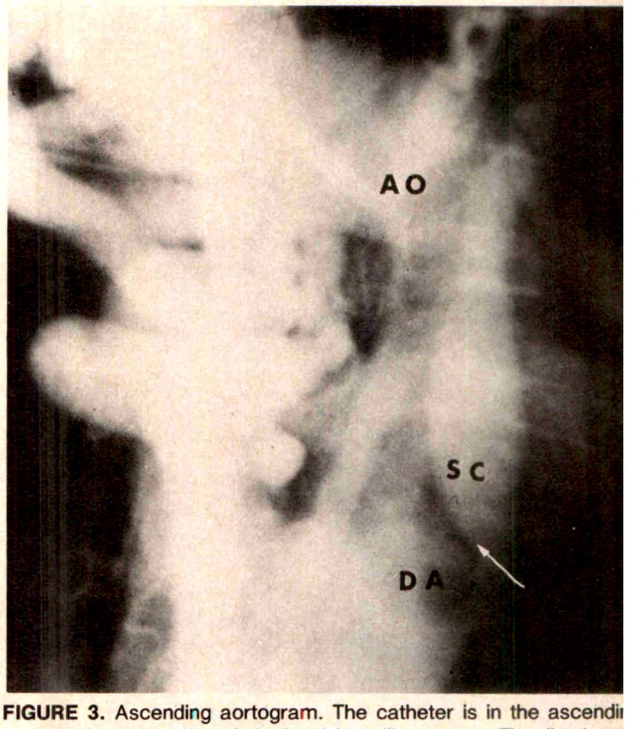

FIGURE 3. Ascending aortogram. The catheter is in the ascendi aorta and was introduced via the right axillary artery. The distal aor is opacified. The left subclavian artery is narrowed at its orig **(arrow)**. AO = aorta; DA = distal aorta; SC = subclavian artery.

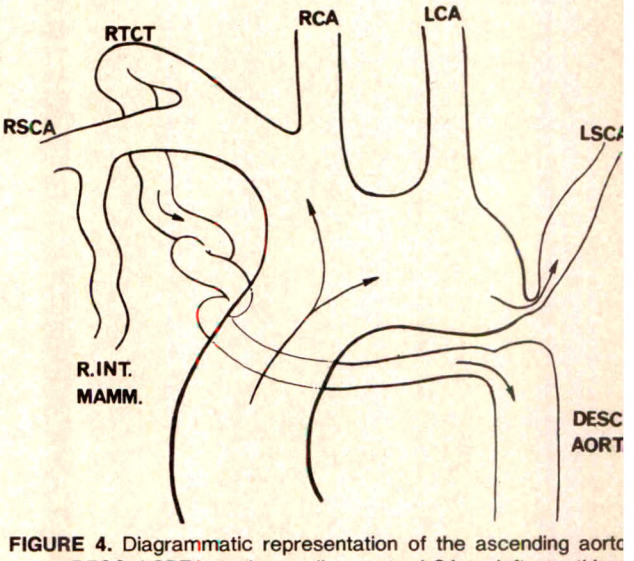

FIGURE 4. Diagrammatic representation of the ascending aortc gram. DESC AORTA = descending aorta; LCA = left carotid ar tery; LSCA = left subclavian artery; RCA = right carotid artery; R INT. MAMM. = right internal mammary artery; RSCA = right sub clavian artery; RTCT = right thyrocervical trunk.

anomaly. About 75 percent of all patients die within the 1st year of life.[27] They invariably have associated cardiovascular malformations. Most commonly these are ventricular septal defect and patent ductus arteriosus, and the combined lesions constitute the so-called triad of Everts-Suarez and Carson.[28]

When total interruption or atresia of the aortic arch is not accompanied by other malformations, survival time is prolonged and the prognosis is much improved. This is undoubtedly due to the formation of effective collateral supply during fetal and early postnatal life. The presence or absence of a patent ductus arteriosus or of other intracardiac shunts has a decisive influence on the formation of such channels.

Importance of patent ductus for survival: Patency of the ductus arteriosus is normal in intrauterine life and favored by the high resistance in the fetal pulmonary vascular bed. Provided that the aorta is normal, the fetus can compensate for the absence of a patent ductus; however, it cannot survive inadequate return of fetal blood to the placenta. Lesions that restrict this return, such as postductal aortic coarctation, are always accompanied by development *in utero* of extensive collateral vascular blood supply. This development is further facilitated by the pre ence of significant pressure differences in the pr and poststenotic segments of the aorta.

On the other hand, if the coarctation is preducta blood is liberally supplied to the descending aor and to the placenta through the normally pate ductus, and intrauterine collateral circulation fails

TABLE III

Anomalies Associated with Postductal Coarctation and Interruption of the Arch of the Aorta

	Postductal Coarctation	Isolated Interruption of the Arch of the Aorta
Patent ductus arteriosus	Absent	Absent
Ventricular septal defect	Absent	Absent
Bicuspid aortic valve	Present	Present
Stenosis of left subclavian artery	Absent	Present

develop. A similar situation exists in complete interruption of the arch of the aorta. In those cases in which a patent ductus arteriosus supplies the descending aorta few if any collateral channels will form. The fetus develops normally, but at birth the infant's survival is severely compromised by an obligatory right to left shunt through the patent ductus.

Analysis of the eight cases of isolated interruption of the aortic arch discloses that a ligamentum arteriosum was identified in five, not mentioned in two[8,14] and "not identified" in one case.[24] It is possible or even likely that a patent ductus arteriosus existed at one time in all eight cases. This argument is strengthened by the extreme rarity of total absence of the ductus arteriosus in the 250 cases of this anomaly on record. There were only two newborn infants[30]* in whom interruption of the aortic arch was accompanied solely by intracardiac anomalies. However, the presence of a patent ductus without intracardiac shunts was reported in 6 of the 250 cases.[24,30–33] All six patients died in the immediate newborn period.

Explanations for ductal closure in survivors: It appears therefore that a persistent patent ductus arteriosus with or without intracardiac anomalies in association with interruption of the arch of the aorta is usually incompatible with prolonged postnatal survival. The question arises why and when does the ductus close in the successful long-term survivors with the isolated anomaly. Normally the ductus arteriosus responds by contraction and functional closure to increased blood arterial oxygen saturation after birth.[34] It seems plausible that a similar mechanism may have been operative in the patients with isolated interruption of the aortic arch. However, the only way oxygenated blood can reach the descending aorta under these circumstances is through collateral vessels that directly or indirectly anastomose the proximal and distal aortic limbs. This necessarily implies the formation of collateral channels before birth in response to a narrow or prematurely closing ductus.

This explanation may apply to all cases of isolated interruption of the aortic arch in which the ductus ligament was found anchored to the descending aorta. It does not apply to the single case in which it joined the ascending aorta.[25] In this instance the ductus in intrauterine life contributed the entire right ventricular output to the aorta, and vascular return to the placenta depended entirely upon collateral vessels carrying blood from the proximal to the distal aortic limb.

Differentiation from postductal coarctation of aorta: The clinical findings in isolated interruption of the aortic arch closely resemble those in so-called adult or postductal coarctation of the aorta. In the latter, the aorta is narrowed at a point just opposite or distal to the orifice of the ductus arteriosus or the insertion of the ductus ligament. As in total interruption of the arch, coarctation is a lesion obstructing the flow of blood to the distal aorta. It is therefore not surprising that extensive collateral channels develop early in life in both anomalies. The characteristic clinical features of hypertension in the ascending aorta and its branches and significant differences in the blood pressure and pulse between the upper and lower limbs are also common to both anomalies. Furthermore, both may be accompanied by a bicuspid aortic valve. Maude Abbott[35] was one of the first investigators to stress this finding and it has since been verified by many observers.[36] Among the eight patients with isolated interruption of the aortic arch, two had a bicuspid aortic valve: One patient[24] had aortic bacterial valvulitis and the other[7]* had severe calcification of the malformed valve. The aortic valve was stated to be normal in three other patients.

On clinical grounds, it is therefore impossible to distinguish patients with isolated interruption of the aortic arch from those with postductal coarctation and a closed ductus arteriosus. However, two anatomic differences between these anomalies might aid in the radiologic diagnosis (Table III). The site of stenosis in postductal coarctation is typically distal to the left subclavian artery, whereas in four of the eight cases of isolated interruption the gap in the arch was proximal to the left subclavian artery (Table II). In the remaining four patients the interruption was immediately distal to it (type A interruption) and in those instances it would be difficult to determine the type of lesion present. However, in one of these three patients[7]* stenosis of the left subclavian artery at its origin from the proximal aorta was noted on angiography. A similar stenosis of the left subclavian artery originating from the distal aortic limb was detected during operative repair in a second patient with the isolated interruption (Type B).[13] Stenosis of the left subclavian artery is not a feature of postductal coarctation.

In conclusion, patients with the isolated type of interruption of the arch of the aorta resemble patients with postductal coarctation in their longevity and their clinical symptoms. The main anatomic features of total interruption of the aorta are its location in the arch and its association with a stenosis of the left subclavian artery. Recognition of these features may be helpful in making the angiographic diagnosis.

* Cases 5 and 7.

* Case 1.

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Electrocardiographic Evidence of Left Ventricular Hypertrophy in Otherwise Normal Children

Clarification by Echocardiography

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Eleven apparently normal children whose electrocardiograms demonstrated greatly increased precordial QRS voltages suggestive of left ventricular hypertrophy were studied by echocardiography to determine whether this finding represented an early manifestation of cardiac disease. Echocardiographic measurements of the thickness of the ventricular septum and of the left ventricular posterobasal wall were normal in all 11 subjects when compared with normal values for age. Also within normal limits were left ventricular, left atrial and aortic root internal diameters, left ventricular mass and the motion and structure of the anterior and posterior mitral valve leaflets. We conclude: (1) These children probably have normal hearts; (2) increased precordial QRS voltage in children and adolescents, in the absence of other abnormalities, is an unreliable indicator of left ventricular hypertrophy; and (3) echocardiography is a powerful diagnostic test in determining the significance of abnormal electrocardiograms suggestive of left ventricular hypertrophy.

The electrocardiographic finding of markedly increased precordial QRS voltages suggesting left ventricular hypertrophy in otherwise normal children often presents a diagnostic dilemma. Whereas such evidence may be an early manifestation of a cardiomyopathy,[1–3] including asymmetric septal hypertrophy,[4] in some instances the voltage criteria used to identify left ventricular hypertrophy in children may be too sensitive and result in a false positive diagnosis. Since echocardiography is a sensitive noninvasive technique particularly useful in measuring ventricular wall thickness, we believed that it could be employed to determine whether in a given child with electrocardiographic evidence of left ventricular hypertrophy an actual increase in left ventricular wall thickness or cavity dilation was present, or whether the heart was in fact normal. As a test of this hypothesis, we performed echocardiographic studies in 11 children previously reported[3] to have unresolved diagnostic problems emanating from the finding of markedly increased electrocardiographic voltages in the precordial leads.

Patient Selection

The study group was composed of 11 children previously reported to have electrocardiograms suggesting left ventricular hypertrophy.[3] Seven other children with similar electrocardiographic findings were lost to follow-up. All subjects were chosen from a large group of children judged to have "innocent" murmurs after routine evaluation at the Johns Hopkins Hospital Children's Cardiac Clinic.[3] Seven were boys and 4 were girls; all 11 children were black. Age at the time of echocardiographic examination ranged from 8 to 18

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TABLE I

Echocardiographic and Electrocardiographic Data in 11 Children

Case no.	Sex	Age (yr)	BSA (m^2)	Precordial QRS Voltages (mm)				Echocardiographic Dimensions (mm)						
				SV_1	RV_5	RV_6	QV_6	Ao (ID)	LA (ID)	PBLV (WT)	VS (WT)	LVd (ID)	LVs (ID)	LV Mass (g)
1	M	6		23	50	31	2							
		10		16	50	30	3							
		12	1.24	17	40	30	3	20	21	7	7	39	28	93
2	M	7		50	33	22	1							
		10		50	35	26	1							
		13	1.64	42	32	22	0	21	25	9	9	43	31	154
3	M	13		30	36	23	3							
		17		27	24	17	2							
		18	1.75	23	20	15	2	17	23	9	9	39	24	131
4	M	11		13	42	29	4							
		16		15	29	20	2							
		17	1.88	9	25	21	3	21	30	9	9	49	39	192
5	F	1		21	38	28	1							
		7		16	34	29	1							
		9	1.15	26	34	30	2	15	21	7	7	41	27	101
6	F	6		46	33	27	1							
		8	1.00	32	30	30	1	13	22	6	6	43	32	90
7	F	8		21	54	35	3							
		10		15	34	30	1							
		12	1.39	18	23	25	1	15	26	7	7	47	30	129
8	M	9		18	34	35	1							
		12		22	21	19	1							
		17	1.76	22	12	12	1	25	23	8	8	48	31	159
9	F	11		11	40	32	2							
		13		22	48	33	2							
		14	1.39	24	46	30	1	21	26	8	8	42	29	127
10	M	3		13	40	29	4							
		10		11	35	25	3							
		11	1.72	12	34	30	3	17	30	8	8	45	27	143
11	M	5		7	35	30	3							
		8	...	14	35	30	3	17	18	8	8	35	27	95

Ao = aorta; BSA = body surface area; ID = internal diameter; LA = left atrium; LV = left ventricular; LVd = left ventricular diameter at end-diastole; LVs = left ventricular diameter at end-systole; PBLV = posterobasal left ventricular wall; VS = ventricular septum; WT = wall thickness.

years (mean 12.6 years). All 11 subjects had precordial QRS voltages (SV_1 or RV_6) that exceeded 3 standard deviations from the mean for age when compared with normal standards.[5] No child had secondary ST-T wave abnormalities. Combined voltage criteria for left ventricular hypertrophy, using summed voltages (for example, SV_1 and RV_6), were not used to select any patient for this study because of the poor reliability of such criteria in children.[6]

Methods

A medical history, physical examination and a standard 12 lead electrocardiogram were obtained in each subject. Recent chest roentgenograms and hematocrit determinations were available for each patient. Echocardiograms were obtained using an Aerotech gamma transducer and a modified Ekoline 20 ultrasonic unit. The signal was connected by a custom-built video amplifier to a Honeywell 1856 Visicorder and recorded continuously on light-sensitive paper. The ventricular septum was measured inferior to the tips of the mitral leaflets just before atrial systole; the posterobasal left ventricular wall was also measured just before atrial systole with the transducer oriented so that part of the ultrasonic beam was reflected from the posterior mitral leaflet. Left ventricular dimensions and wall thickness were compared with normal standards.[7] Left ventricular mass was derived from the echocardiographic measurements by the method of Troy et al.[8]

Results

Echocardiographic and electrocardiographic data for the 11 subjects are summarized in Table I. All subjects were asymptomatic and had no history of cardiovascular disease or anemia; physical examination, blood pressure and hematocrit determinations were normal in each child. All subjects had an innocent grade 1-2/6 systolic ejection murmur. Chest roentgenograms were normal in nine subjects and were interpreted as showing a slight increase in the cardiac silhouette in two (Cases 7 and 11).

Echocardiographic measurements of the thickness of the ventricular septum and of the left ventricular posterobasal wall were normal in all 11 subjects when

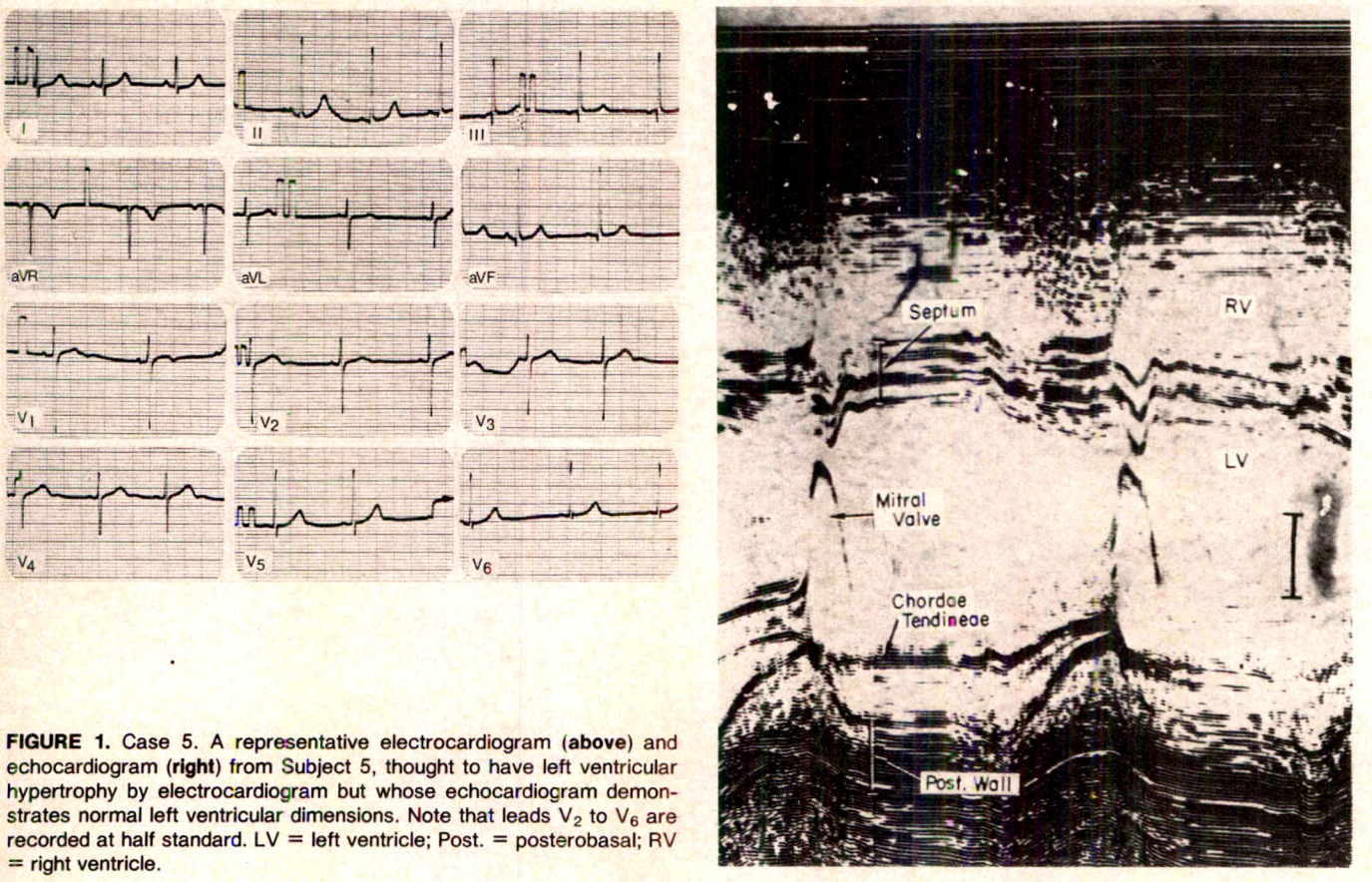

FIGURE 1. Case 5. A representative electrocardiogram (**above**) and echocardiogram (**right**) from Subject 5, thought to have left ventricular hypertrophy by electrocardiogram but whose echocardiogram demonstrates normal left ventricular dimensions. Note that leads V_2 to V_6 are recorded at half standard. LV = left ventricle; Post. = posterobasal; RV = right ventricle.

compared with normal values for age. Ventricular septal thickness ranged from 6 to 9 mm (mean 7.8 mm; normal range 6 to 9 mm). Posterobasal left ventricular wall thickness similarly ranged from 6 to 9 mm (mean 7.8 mm; normal range 6 to 9 mm). Also within normal limits were left ventricular, left atrial and aortic root internal diameters, left ventricular mass, and the motion and structure of the anterior and posterior mitral valve leaflets.

At the time of this study, 8 of the 11 subjects still had abnormally tall precordial QRS voltages suggestive of left ventricular hypertrophy; in the 3 other subjects (Cases 3, 4 and 8), precordial voltages had diminished, now falling into the limits of normal. There was no relation between ventricular wall thickness and precordial voltage in the 11 subjects. Figure 1 shows a representative echocardiogram and electrocardiogram from one subject (Case 5).

Discussion

Since left ventricular wall thickness can be measured directly by echocardiography, it seemed reasonable to apply this technique to resolve the diagnostic ambiguities often raised by commonly used electrocardiographic criteria for left ventricular hypertrophy in children and adolescents. The 11 subjects studied were chosen since their cases had previously been reported as examples of the difficulty encountered in determining whether large precordial QRS voltages in children indicate myocardial hypertrophy or represent false positive diagnoses of left ventricular hypertrophy. Echocardiographic studies in all 11 subjects demonstrated normal wall thickness, cavity dimensions and left ventricular wall mass. These findings indicate that precordial voltage criteria for the electrocardiographic diagnosis of left ventricular hypertrophy in children and adolescents are unreliable and that measurements of left ventricular dimensions by echocardiography may provide superior specificity for the diagnosis of left ventricular hypertrophy.

The width of the ultrasonic beam, as employed in conventional one-dimensional echocardiography, is rather narrow and allows visualization of only a small portion of the ventricular septum and posterobasal left ventricular free wall. Thus, it is possible that eccentric hypertrophy of the left ventricle may elude detection. However, to our knowledge no cardiac diseases have been described that might present with hypertrophy of portions of the left ventricle not accessible to the ultrasonic beam.

In addition to having high specificity in detecting left ventricular hypertrophy, echocardiography also appears to be an extremely sensitive method of detecting this abnormality. Extensive use of this technique in the Cardiology Branch of the National Heart and Lung Institute has resulted in the diagnosis of many instances of asymmetric hypertrophy of

the ventricular septum,[4] even when results of all other noninvasive studies, including electrocardiography, were within normal limits.[9] Moreover, we have seen many patients with hemodynamically documented severe aortic stenosis who had no electrocardiographic evidence of left ventricular hypertrophy, but who nonetheless had thickened left ventricular walls demonstrated by echocardiography. Although the patients in this study were all black children, the approach used was direct measurement of ventricular wall thickness by echocardiography, and there is no reason to expect that our data are not applicable to all patient populations.

It is obvious that more prolonged follow-up studies of subjects similar to ours, or necropsy correlation of echocardiographic with electrocardiographic findings, will be necessary to determine definitely the relative merits of these two techniques in establishing the diagnosis of left ventricular hypertrophy in children and adolescents. The data presented in this study and others suggest that echocardiography will prove the more sensitive and specific method.

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Electrophysiologic Effects of the Antiarrhythmic Agent Disopyramide Phosphate

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The electrophysiologic effects of the antiarrhythmic agent disopyramide phosphate given intravenously were studied in 10 patients with cardiac disease. Studies included determinations of sinus recovery time and refractoriness of the atria, the atrioventricular (A-V) node and the His-Purkinje system. Measurements were performed at rest and 15 and 30 minutes after administration of disopyramide. Serum drug levels were measured at these times.

Sinus recovery time was shortened at both 15 and 30 minutes, with an average decrease of 39.5 and 146.2 msec, respectively ($P < 0.01$). Atrial refractoriness was not altered significantly, but tended to be reduced; the mean effective refractory period was 289.5 msec before administration of disopyramide and 259 and 270 msec 15 and 30 minutes, respectively, after administration. The functional refractory period of the atrioventricular (A-V) node was definitely prolonged in seven patients 15 minutes after administration of disopyramide. The relative refractory period of the His-Purkinje System was not altered.

Although this study does not elucidate the mechanism by which disopyramide achieves its antiarrhythmic effects, animal work has shown that it is similar to that of quinidine. In the doses used the drug does not seem to cause first, second or third degree A-V block or fascicular or bundle branch block; it did not increase the severity of first degree A-V block in the three patients with this disturbance. The drug may be particularly useful when arrhythmias are associated with slow sinus rates.

Disopyramide phosphate, a synthetic compound, has been demonstrated to have significant antiarrhythmic properties.[1,2] Few antiarrhythmic agents have been added to the therapeutic armamentarium in recent years,[3–5] and the search for effective agents has continued. Mokler and Van Arman[6] first described the antiarrhythmic properties of disopyramide.

There is a need for new agents that combine effectiveness with a low incidence of side effects so that they can be administered over extended periods, primarily to treat and prevent life-threatening arrhythmias. Quinidine and procainamide are widely used preparations but they have many side effects and are not well tolerated by many patients.[7]

Disopyramide phosphate, unrelated chemically to any of the conventional antiarrhythmic agents, is available for both oral and parenteral administration. The oral preparation has been used extensively overseas.[8–11] To evaluate the effects of this drug on electrophysiologic variables in man, as has been done with other antiarrhythmic agents,[3,12] we administered it intravenously to patients with heart disease in pharmacologically meaningful doses.

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	Type of Heart Disease	Electrocardiogram
1	47M	Cardiomyopathy	NSR; IRBBB
2	46M	Cardiomyopathy	NSR; ST–T wave changes
3	47M	ASHD	NSR; inferior and anterior wall myocardial infarctions
4	58M	ASHD	NSR; premature beats
5	73M	ASHD	NSR; 1st° A–V block; left anterior hemiblock; multiple PVCs
6	27M	Chest pain Normal coronary arteriogram	NSR; ST–T wave changes
7	77M	ASHD	NSR; 1st° A–V block; multiple PVCs
8	51M	ASHD	Sinus bradycardia; 1st° A–V block
9	77M	ASHD	NSR; 1st° A–V block; multiple PVCs
10	49M	Cardiomyopahty	NSR; WNL

ASHD = arteriosclerotic heart disease; IRBBB = incomplete right bundle branch block; NSR = normal sinus rhythm; PVCs = premature ventricular contractions; WNL = within normal limits.

Material and Methods

Disopyramide phosphate (Norpace [c], G. D. Searle Laboratories) was administered intravenously (2 mg/kg body weight) to 10 male patients with various types of heart disease (Table I). Patients were studied, after informed consent was obtained, during diagnostic cardiac catheterization and before the administration of contrast agents. Some of the patients had extrasystoles at the time of the study; all had sinus rhythm.

Electrophysiologic measurements included determinations of sinus recovery time[13,14] and refractory periods of the atria, the A–V node and the His-Purkinje tissue as studied by the extrastimulus technique[15] during continuous atrial pacing at a rate slightly faster than the underlying sinus rate. The extrastimulus was applied every eighth beat and was followed by an appropriate delay to avoid repetitive firing. Diastole was scanned progressively with a programmed stimulator (Bio-Celestronix) that simultaneously paced the right atrium at a fixed rate and introduced a premature impulse every eight beats. Simultaneous bipolar recordings from the His bundle area, local right ventricular apex and right atrium were obtained with filter settings at 50 and 400 hertz, as previously reported by this laboratory.[15] Four surface electrocardiogram leads (leads I, II, aVF and V_1) were recorded simultaneously.

The stimulator delivered impulses of 1.5 msec duration and the energy output was set at approximately twice diastolic threshold. Continuous atrial pacing was started at a rate slightly faster than the patients' sinus rate to avoid the effect of changing cycle length on refractoriness. After control measurements were made, disopyramide phosphate was administered as a bolus injection over a 5 minute period in a dose of 2 mg/kg body weight. Measurements were repeated 15 and 30 minutes after completion of the injection. Blood levels of the drug were determined before administration of the drug and 15 and 30 minutes after administration. The data were recorded on photographic paper at a paper speed of 100 mm/sec on a 16 channel Electronics for Medicine apparatus and also stored on magnetic tape for later review by two separate observers for the purpose of this study. Simultaneous measurements of cardiac output and other hemodynamic variables were made in selected patients.

Definition of Terms

The following terms are used:

Sinus recovery time is the interval between the last paced beat and the first spontaneous sinus beat, after a minimum of 2 minutes of overdrive suppression of the sinus node[13,14] at a rate faster than the sinus rate.

A is the local right atrial electrogram.

H is the His bundle potential recorded with bipolar electrodes 1 mm apart.

V is the earliest recorded ventricular activity taken from either the surface leads or the intracardiac electrograms.

St_1 is the continuous or driving stimulus.

St_2 is the testing or premature stimulus.

The A–H interval is the measure of A–V nodal conduction time (normal 50 to 120 msec).

The H–V interval is the measure of His-Purkinje conduction time (normal 35 to 55 msec).

The effective refractory period of the atria is defined as the longest S_1–S_2 interval at which S_2 fails to produce atrial depolarization.

The functional refractory period of the atria is measured as the shortest recorded A_1–A_2 interval.

The effective refractory period of the A–V node is measured as the longest A_1–A_2 interval at which A_2 fails to produce an H_2.

The functional refractory period of the A–V node is the shortest H_1–H_2 interval recorded.

The relative refractory period of the His-Purkinje system is the longest H_1–H_2 interval at which H_2 conducts to the ventricles with a longer H–V interval than that of the basic driving beat or in which the QRS complex has an aberrant configuration. This definition implies that the main left bundle and its fascicles and the entire right bundle act as a single physiologic unit.

Results

The results are summarized in Tables II to V. Resting A–H and H–V intervals were not altered by disopyramide.

Sinus recovery time: This period was reduced in all patients 15 and 30 minutes after administration of disopyramide (Table II). The change was more pro-

TABLE II

Sinus Recovery Time (msec)

Case no.	Control	Minutes After Disopyramide 15	30
1	1020	900	920
2	1080	890	830
3	950	...	915
4	1340	1290	...
5	1190	920	925
6	1025	980	970
7	1190	1090	1050
8	1210	1180	890
9	700	...	600
10	1040	950	900
Mean	1074.5	1035	888.8
± SD	±164	±147	±124
P value		<0.01	<0.01

P = probability; SD = standard deviation

nounced after 30 minutes. Average sinus recovery time was 1,074.5 msec at rest, 1,035 msec at 15 minutes (a 3.6 percent change), and 888.8 msec at 30 minutes (a 17.2 percent change). Figure 1 shows an example with a reduction from 1,190 to 920 msec in 15 minutes. The differences were statistically significant ($P < 0.01$) for both the 15 and 30 minute studies. The basic underlying sinus rate was not altered by the drug.

Atrial refractoriness: The effective refractory period of the atria was decreased after disopyramide in five patients, unchanged in two and increased in two; the study was not performed in one patient (Table III). These changes were not statistically significant; however, the mean effective refractory period tended to be decreased (289.5 msec before disopyramide and 259 and 270 msec 15 and 30 minutes, respectively, after disopyramide). The functional refractory period of the atria after disopyramide was decreased in four, unchanged in two and increased in

TABLE III

Effects of Disopyramide on Atrial Refractory Periods (msec)

Case no.	Paced Cycle Length	Effective Refractory Period			Functional Refractory Period		
		Control	Minutes After Disopyramide 15	30	Control	Minutes After Disopyramide 15	30
1	690	310	360	305	310	290	270
2	695	300	300	300	360	335	...
3	690	350	250	205	310	305	265
4	1020	350	...	...	305	345	...
5	880	305	...	375	305	...	305
6	880	320	190	...	280	255	...
7	960	240	230	...	340	360	345
8	1100	240	245	220	300	340	330
9	990	230	230	220	330	340	320
10	840	250	265	265	280	290	270
Mean		289.5	259	270	312	318	301
± SD		±46	±45	±61	±25	±27	±20

TABLE IV

Effects of Disopyramide on A-V Nodal Refractory Periods (msec)

Case no.	Paced Cycle Length	Effective Refractory Period			Functional Refractory Period		
		Control	Minutes After Disopyramide 15	30	Control	Minutes After Disopyramide 15	30
1	690	310	360	305	485	535	490
2	695	360	...	...	460	460	...
3	690	335	350	360	470	505	525
4	1020	390	410	...	490	505	490
5	880	325	300	...	410	425	440
6	740	325	300	...	410	425	...
7	960	395	370	380	620	630	640
8	1100	360	345	330	565	515	500
9	990	330	350	355	455	470	500
10	840	...	...	...	545	450	440
Mean		348	348	348	491	492	503
± SD		±30	±32	±31	±49	±62	±63

four. The changes were not statistically significant.

A–V nodal refractoriness: The effective refractory period of the A–V node was prolonged in four patients, shortened in four and not tested in two 15 minutes after administration of disopyramide; it was shortened in three, prolonged in two and not tested in five 30 minutes after administration (Table IV). The differences were insignificant.

The functional refractory period of the A–V node was prolonged in seven patients, shortened in two and unchanged in one 15 minutes after disopyramide; it was unchanged in two, prolonged in four and shortened in two 30 minutes after drug administration. The differences were small and not statistically significant for the effective refractory period but at 15 minutes the functional refractory period was definitely prolonged in seven patients, as shown previously in dogs.[18]

His-Purkinje system refractoriness: The relative refractory period of the His-Purkinje system was not altered by the drug since no prolongation of the H–V interval or widening of the QRS complex was noted either 15 or 30 minutes after administration of disopyramide.

Arrhythmias: In three patients the rate of ventricular premature beats was reduced from 10 to 15/min at the beginning of the study to 2 to 3/min at 15 minutes and to 1 to 2/min at 30 minutes. In another patient, short bursts of atrial fibrillation were induced electrically during the control period of atrial premature stimulation. When the impulse was discharged during the atrial vulnerable period, atrial fibrillation occurred repeatedly. After administration of disopyramide, a similar timed stimulus failed to induce atrial fibrillation, thus suggesting that the drug elevated the atrial fibrillation threshold (Fig. 2).

Serum drug levels: The mean serum levels of disopyramide as determined by the gas chromatographic method were 1.56 g/ml (range 0.82 to 2.30) at 15 minutes and 1.51 g/ml (range 1.19 to 1.83) at 30 minutes.

TABLE V

Serum Concentration of Disopyramide (μg/ml)*

Case no.	Control	Minutes After Administration 15	30
1	...	...	...
2	0	1.08	...
3	0	1.20	...
4	...	2.12	1.83
5	0	1.66	1.33
6	0	2.00	...
7	0	1.20	1.4
8	0	0.82	...
9	0	2.30	1.82
10	0	1.67	1.19
Mean		1.56	1.51
± SD		±0.52	±0.29

* Determination performed by the gas chromatography method by Azur Karim, PhD, Department of Biochemical Research, Searle Laboratories, Chicago.

Discussion

When given intravenously, disopyramide has a two phase disappearance curve. The first or so-called distribution phase, which reflects equilibrium between

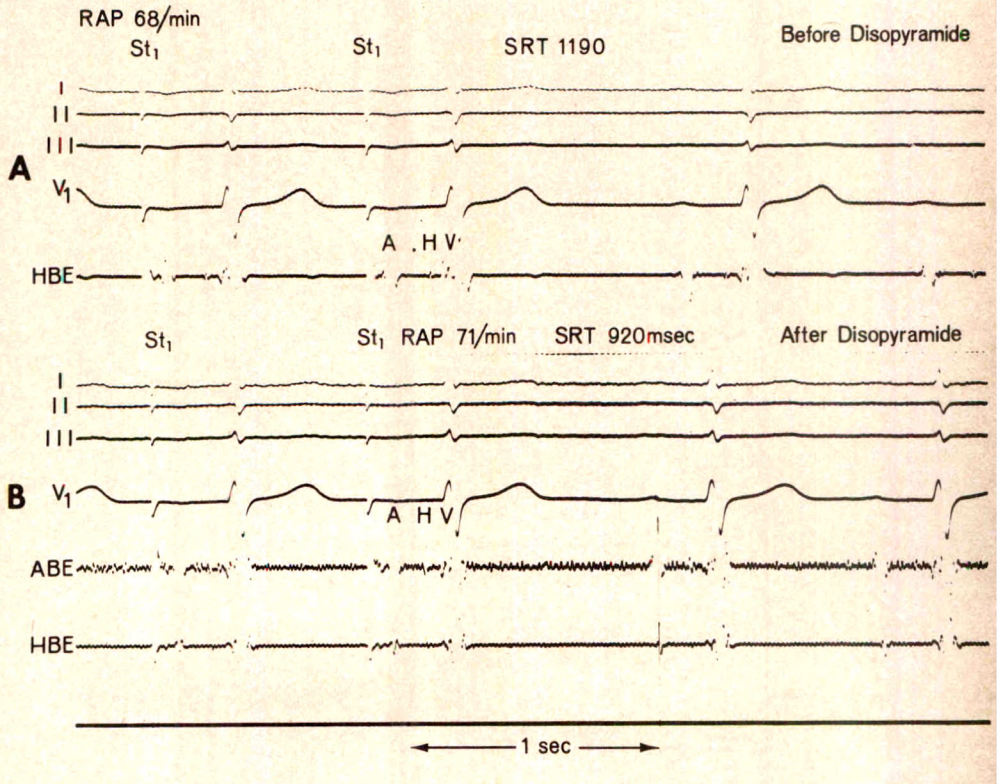

FIGURE 1. A, leads I, II, III and V_1 of electrocardiogram and His bundle electrogram (HBE). Sinus recovery time (SRT) before administration of disopyramide in 1,190 msec. **B,** same as **A** plus atrial bipolar electrogram (ABE) recorded 15 minutes after disopyramide. SRT is 920 msec. RAP = right atrial pacing.

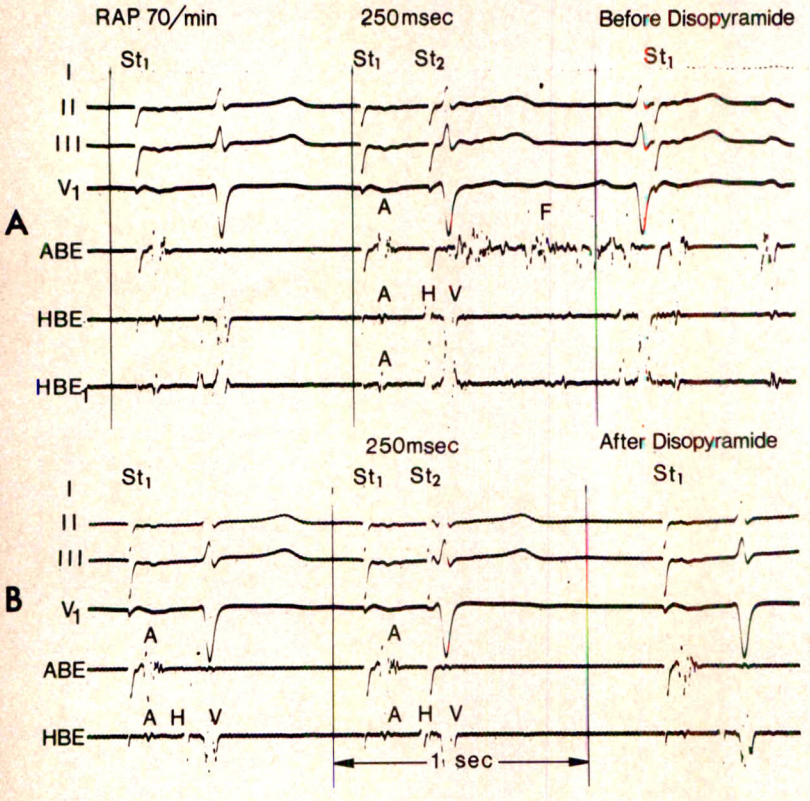

FIGURE 2. A, run of atrial fibrillation (F) after coupled atrial pacing at an St_1–St_2 interval of 250 msec before administration of disopyramide. **B,** same coupling interval of 250 msec does not result in atrial fibrillation after disopyramide. Abbreviations as in Figure 1.

tissue content and the vascular space, has a half-life of 20 to 30 minutes. The second or excretory phase, which reflects the disappearance of the drug from the body once tissue equilibrium has occurred, has a half-life of 2 hours.[1] Our physiologic studies were performed 15 and 30 minutes after completion of infusion, well within the range of the distribution phase. The actually measured mean blood levels were 1.56 μg/ml at 15 minutes and 1.54 μg/ml at 30 minutes.

According to Ranney et al.,[1] the oral preparation is almost completely absorbed from the gut and rapidly eliminated in the urine and feces. After peak blood levels were reached, the biological half-life in men was about 7 hours, indicating that frequent oral doses are required to maintain a therapeutic blood level.

Antiarrhythmic agents like quinidine or procainamide exert their effects by a myocardial depressant action, hence decreasing excitability, conduction velocity and contractility.[7] Mathur[2] has suggested that disopyramide also exerts its antiarrhythmic effect by these mechanisms.

Excitability: Quinidine elevates the threshold to electrical stimuli and abolishes or depresses impulse formation by this mechanism. This effect was not directly tested in our study with disopyramide but it appears likely that this is the mechanism by which the drug reduced the frequency of premature beats in the three patients who manifested this arrhythmia at the onset of the study.

Refractory periods: Quinidine in a concentration of 6 mg/liter produced a 50 percent increase in effective refractory period in the isolated rabbit atria.[16] Similar effects have been reported in isolated ventricular muscle and Purkinje fibers.[17] In the intact dog, quinidine at doses of 5 to 10 mg/kg causes a significant prolongation of the refractory periods of the atria in intact man. After administration of disopyramide the effective refractory period of the atria tended to decrease.

The A–V nodal functional refractory period was prolonged in seven of the nine patients tested. Refractoriness of the His-Purkinje tissue was not altered at the dose of 2 mg/kg. Larger doses were not used since it is known[2] that significant myocardial depression may occur when disopyramide is given at doses greater than 5 mg/kg. In the isolated rabbit preparation, disopyramide increased refractoriness in the atria and A–V node in a manner similar to that of quinidine.[18]

Conduction velocity: Other antiarrhythmic agents like quinidine increase the conduction interval of isolated atria, Purkinje fibers and ventricular muscle and decrease the slope of the action potential.[17] The effect of disopyramide on this property is similar to that of quinidine. In the intact dog,[2] when doses of 1 to 10 mg/kg were used, this effect was less pronounced with disopyramide.

Mechanism of action of disopyramide: Our study has not elucidated the means by which disopyramide exerts its effects. Studies of isolated myocardial cells[18] have suggested that this drug's mode of action is similar to that of quinidine and consists of slowing the rate of rise of the transmembrane action potential by reduction of the overshoot potential and lengthening of the effective refractory period of the A–V node. These effects are shared by disopyramide,

as demonstrated in the isolated rabbit heart[4] and as suggested by the prolongation of the functional refractory period of the A–V node in 7 of our 10 patients.

This study demonstrated that at the doses used, and at serum levels of 0.82 to 3.20 g/ml, no significant alteration of refractoriness and conduction at the level of the atria or His-Purkinje system occurred, but the functional refractory period of the A–V node was generally prolonged. Furthermore, there were no serious clinical conduction disturbances such as first, second or third degree A–V block or fascicular or bundle branch block, even in patients with first degree A–V block (Cases 5, 7 and 9) and left anterior hemiblock (Case 5). The evidence presented here does not imply that when the drug is given in larger doses these changes may not occur.

Clinical implications: The sinus recovery period, a measure of sinus nodal function,[13] was consistently shortened. This property, which may be related to the adrenergic or vagolytic[20] action of disopyramide, enhances the value of this drug in patients with sinus bradycardia.

Although our study was not designed to evaluate systematically the effects of disopyramide in clinical arrhythmias, we found that administration of the drug reduced the incidence of spontaneous ventricular extrasystoles. The mechanism of this action is not known and awaits further study. In one case disopyramide appeared to have raised the atrial fibrillation threshold.

Our findings indicate that the antiarrhythmic effect of disopyramide is not related to its effect on the refractory periods of the atrium or the His-Purkinje tissue but that in addition to its myocardial depressant effect, its prolongation of the functional refractory period of the A–V node may interfere with reciprocating rhythms and result in a beneficial effect.

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Concealed His Bundle Extrasystoles in Congenital Heart Disease

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His bundle electrograms were recorded in two children with cardiac conduction disturbances. In the surface electrocardiograms of one patient His bundle extrasystoles mimicked atrial nonconducted bigeminal rhythms; in the other, they simulated second degree atrioventricular (A-V) block and conducted junctional extrasystoles. In both instances the conduction disturbance was a result of concealed conduction of the His bundle extrasystole into the A-V junction. We conclude that the surface electrocardiogram is suggestive but not definitive in diagnosing His bundle extrasystoles and that His bundle recordings are indispensable for correct diagnosis and treatment.

The phenomenon of concealed conduction has been known since 1911.[1] A clinical electrocardiographic description of premature beats arising in the junctional tissue first appeared in a report by Lewis and Allen.[2] In 1945 Holtzman[3] described extrasystoles that he assumed were arising in the bundle of His. Langendorf et al.[4–7] extensively reviewed the subject and proposed that nonconducted junctional premature systoles could simulate first and second degree atrioventricular (A-V) block, nonconducted atrial premature beats and alteration of the P-R interval by virtue of concealed conduction to the A-V node.[4,7] Similar clinical records of extrasystoles ascribed to the mainstem His bundle have revealed the same phenomenon.[8–10]

Because the concept of concealed bundle of His extrasystoles could not be proved on the basis of the clinical electrocardiogram,[8–12] more interest was displayed in His bundle extrasystoles appearing in experimental studies.[13–17] The recently introduced technique of His bundle recordings in man[18,19] made it possible for Massumi[20] to document the first instance of interpolated extrasystoles arising in the main bundle of His.

This report deals with two patients whose bundle of His recordings documented concealed bundle of His extrasystoles that simulated nonconducted atrial beats and type II A-V block. It is the first report to document His bundle extrasystoles in children, and adds two more cases to the three previously documented cases in adults.[20–22] The study is also the first to demonstrate the occurrence of His bundle extrasystoles during bigeminal rhythm, and it confirms the surface electrocardiographic findings in the study of cardiac conduction and rhythm disturbances in congenital heart disease.

Patients and Methods

Case 1: The first patient was a 6 year old cyanotic girl with tetralogy of Fallot. The surface electrocardiogram demonstrated sinus rhythm, right axis deviation, right ventricular hypertrophy and nonconducted atrial premature beats. During right heart catheterization, His bundle electrograms were recorded by conventional techniques.[18,19] The low right atrium to His potential interval (LRA-H) was measured from the onset of the low right atrial depolarization to the first rapid deflection of the His bundle potential. The His to

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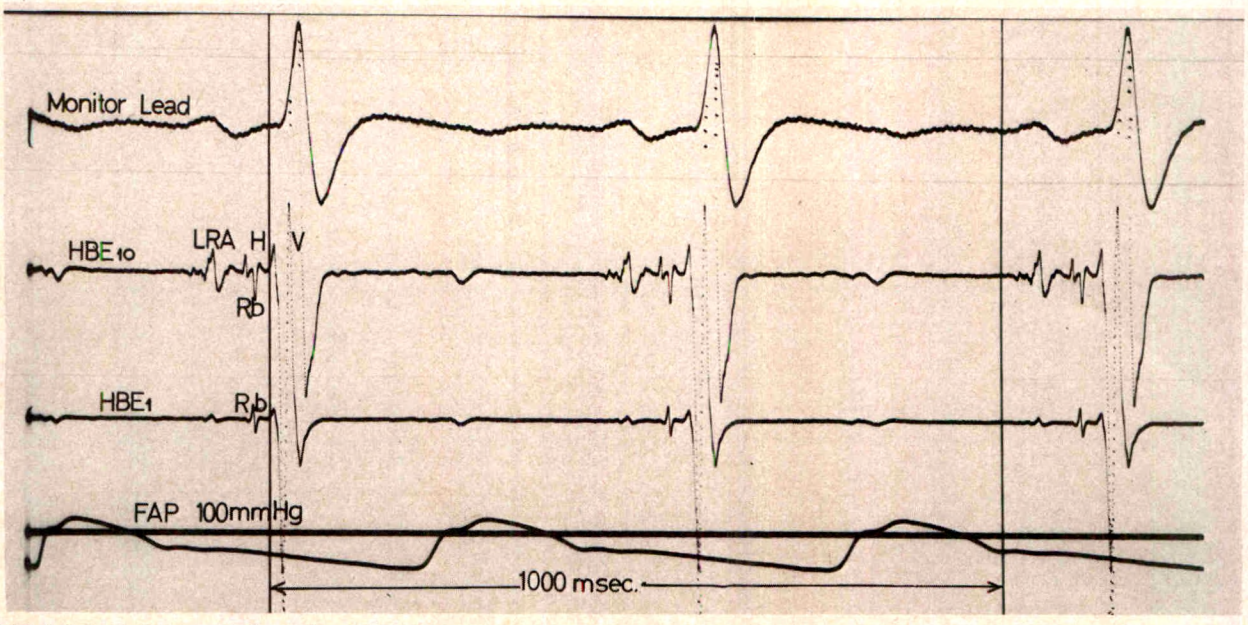

FIGURE 1. Case 1. Representative strip of His bundle electrogram (HBE). **From top to bottom:** monitor lead, His bundle electrogram with 10 mm interelectrode distance, His bundle electrogram with 1 mm interelectrode distance and femoral arterial pressure tracing (FAP): Paper speed is 200 mm/sec; time lines 1,000 msec. Sinus rhythm is present at a cycle length (H-H interval) of 568 msec. The interval from the low right atrium to His potential (LRA-H) is 76 msec, the H-V interval is 37 msec and the Rb-V interval is 24 msec.

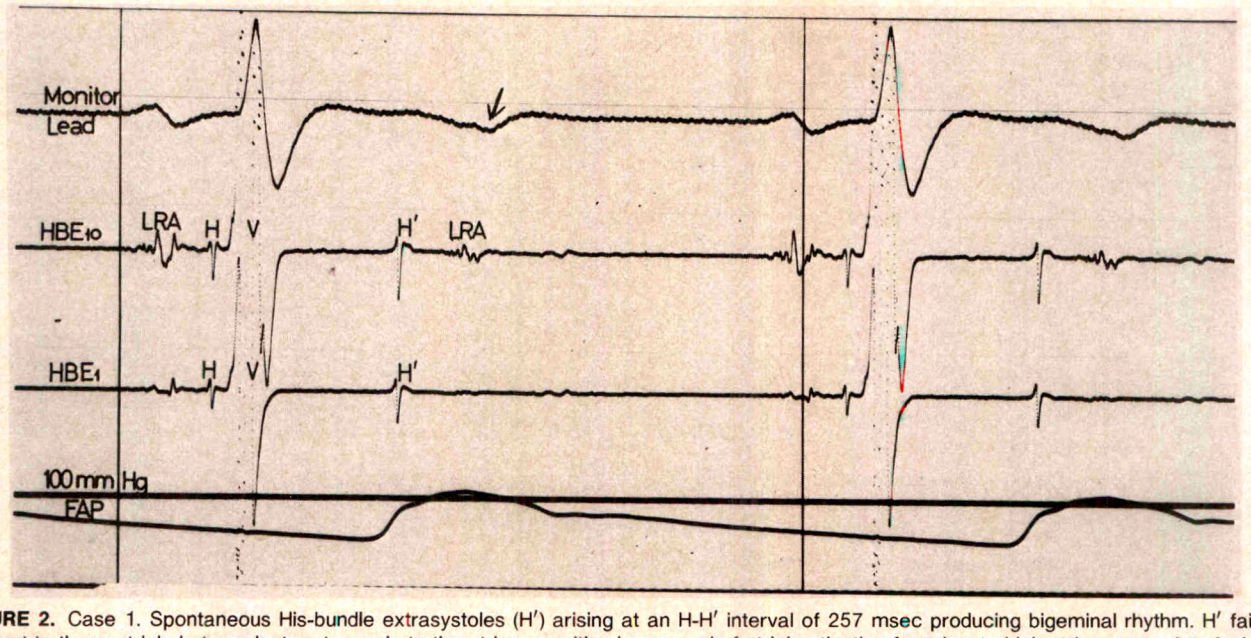

FIGURE 2. Case 1. Spontaneous His-bundle extrasystoles (H′) arising at an H-H′ interval of 257 msec producing bigeminal rhythm. H′ fails to conduct to the ventricle but conducts retrograde to the atrium resulting in reversal of atrial activation from low to high atrium, associated with an inverted P wave **(arrow).** The bigeminal His bundle extrasystoles cause a marked slowing of ventricular rate (compare Fig. 1).

ventricle (H-V) interval was measured from the first rapid deflection of the bundle of His potential to the earliest ventricular activity observed in surface or intracardiac recordings. The right bundle to ventricle (Rb-V) interval was measured from the first rapid deflection of the potential after the His deflection to the earliest ventricular activity. Basic cycle length was measured as the interval between His potentials (H-H interval). All intervals were measured in milliseconds.

Several cardiac cycles were analyzed. At a sinus cycle length of 568 msec, the LRA-H interval was 76 msec (normal 60 to 129); the H-V interval was 37 msec (normal 30 to 55); the Rb-V interval was 24 msec (normal 16 to 36) (Fig. 1). The His potential occurred between the atrial and the ventricular electrograms of conducted beats. In addition, a spontaneous bundle of His extrasystole (H′), similar in contour to the H potential, arose at an interval of 258 msec from the preceding H potential (Fig. 2). The His bundle extrasystole failed to conduct antegrade but conducted retrograde to the atrium, resulting in reversal of the normal sequence of atrial depolarization, associated with an inverted P wave in the descending limb of the T wave. Retrograde depolarization was further confirmed by a high right atrial recording (Fig. 3). The demonstrated nonconducted atrial

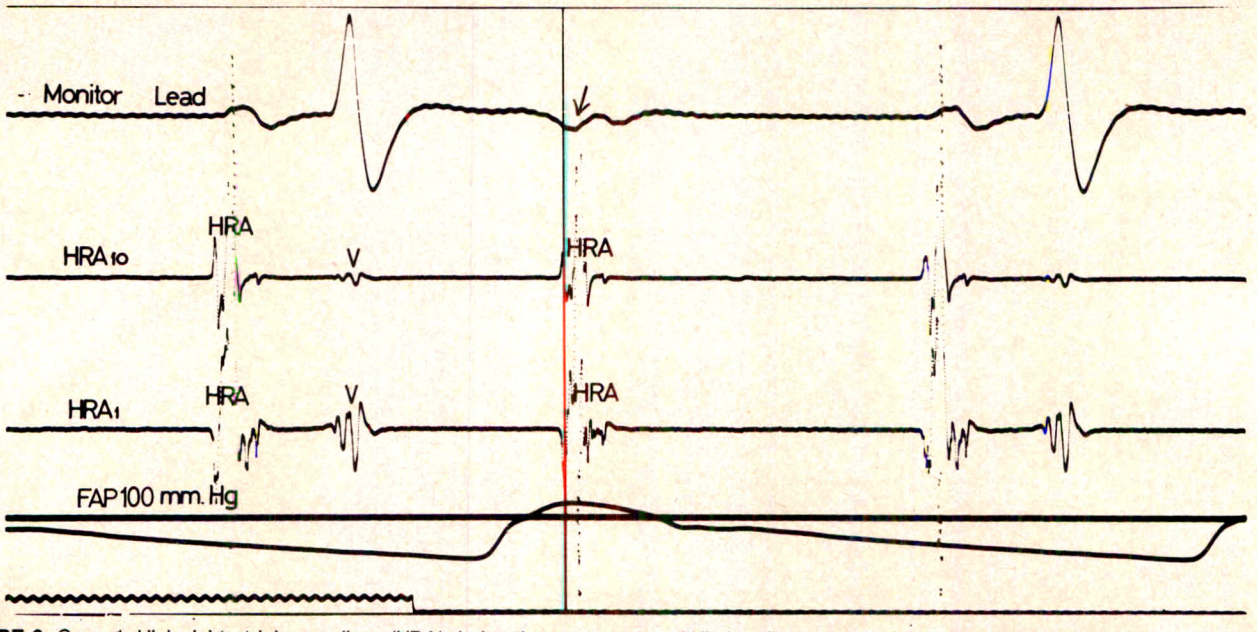

FIGURE 3. Case 1. High right atrial recordings (HRA) during the occurrence of His bundle extrasystoles in bigeminal rhythm. The presence of a nonconducted inverted P wave in the monitor lead on the T wave is proved with simultaneous recordings from high right atrium (HRA_{10} and HRA_1).

bigeminal beats in the surface electrocardiogram had been interpreted as nonconducted premature atrial systoles.

Case 2: The second patient was a 3 year old cyanotic girl with dextrocardia, double outlet right ventricle, pulmonary stenosis and functioning aortic-pulmonary shunt with congestive heart failure. Seven days after total intracardiac repair probable type II A-V block and junctional extrasystoles were noted in the electrocardiogram (Fig. 4). Administration of digoxin, which had been started immediately postoperatively, was discontinued for 2 days because of the possibility of digitalis intoxication. The premature beats and type II A-V block continued. His bundle recordings were performed to elucidate the mechanism of the A-V block. The His bundle electrogram demonstrated only conducted His bundle premature beats of the same configuration as those seen previously in the surface electrocardio-

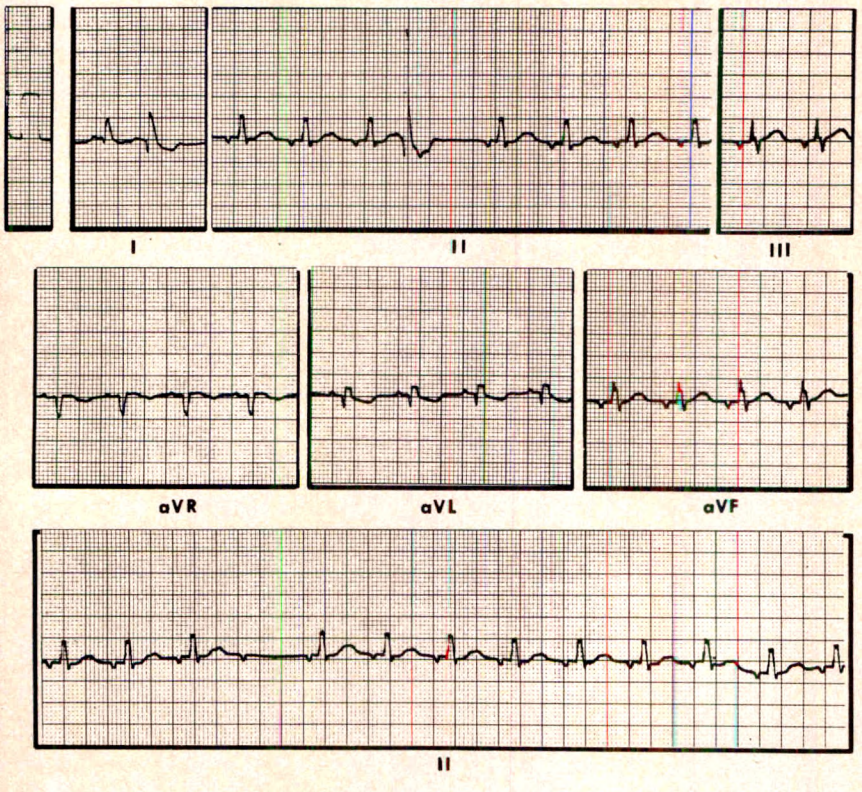

FIGURE 4. Case 2. Representative strips of the electrocardiogram showing low atrial rhythm. In lead II **(top),** the fourth beat is a premature beat with a nonconducted P wave in the S-T segment. In lead II **(bottom),** the fourth beat is blocked without preceding P-R prolongation, suggesting type II A-V block (Mobitz II).

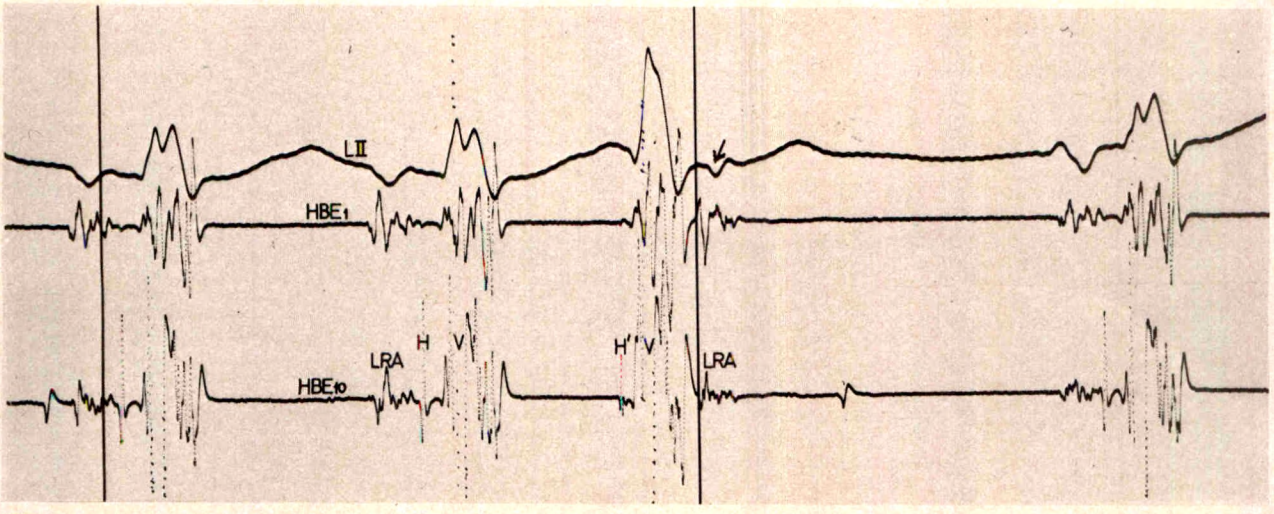

FIGURE 5. Case 2. His bundle recording showing a His extrasystole (H′) that occurs 321 msec after the preceding His deflection and is conducted aberrantly with a right bundle branch block pattern. Retrograde depolarization of the A-V junction and atrium is manifested by the subsequent P wave, which is hidden in the S-T segment. The H′-V interval is slightly shortened.

gram (Fig. 4). The H potential occurred between the atrial and ventricular electrograms of conducted beats. His bundle extrasystoles (H′), similar in contour to the H potential, occurred between the ventricular electrogram of the preceding beat and another ventricular depolarization complex (Fig. 5). This His bundle extrasystole (H′) was not related to the preceding LRA-H interval and occurred 321 msec after the preceding H potential. However, there was a definite relation between the His extrasystole (H′) and the cardiac cycle following it. The His extrasystole (H′) propagated to the ventricle with aberrant conduction, and the subsequent P wave was blocked. It is possible that H′ originated in a fascicle rather than in the common bundle, since the H′-V interval was shorter than the H-V interval and the subsequent QRS complex was aberrant. The tracing resembles that of type II A-V block (Mobitz II). No intrinsic disturbance of A-V conduction was present. The LRA-H and H-V intervals of beats not interfered with were normal, and second degree A-V block would not have been simulated if premature His bundle depolarization had not occurred. Because of these studies, we felt safe in reinstituting administration of digoxin; the remainder of the patient's course was benign.

Discussion

Rosen et al.[21] described a patient who manifested sudden P-R prolongation and periods suggestive of first and second degree A-V block by virtue of concealed conduction of bundle of His extrasystoles. The term pseudo A-V block was initially used by Langendorf et al.[23] and later by Rosen et al.[21] to describe this arrhythmia because there was no evidence of an intrinsic abnormality of A-V conduction. Cannom et al.[22] described a patient whose bundle of His recordings documented that concealed bundle of His extrasystoles simulated nonconducted atrial premature beats; likewise Damato[24] and Wit[25] and their coworkers provided experimental validation that His bundle extrasystoles could simulate types I and II A-V block, high degree A-V block, nonconducted atrial bigeminal rhythm and alteration of the P-R interval.

The cause of His bundle extrasystoles is not yet determined. Neither parasystole nor reentrant activation appear to explain the random and variable occurrence of these extrasystoles in the cardiac cycle. The effect of their occurrence on the subsequent cardiac cycle is related to the temporal relation between the His bundle extrasystole and the refractory period of the A-V specialized conduction system. Greater conduction disturbance occurs when the His extrasystole falls later in the cardiac cycle. Rosen et al.[21] found that the closer to the subsequent P wave the His extrasystole occurred, the more refractory the A–V junction became until there was complete disappearance of the conducted atrial impulse.

Clinical diagnosis: Clinical and experimental validation that His bundle extrasystoles could simulate types I and II and high degree A-V block, nonconducted atrial beats and alteration of the P-R interval have been provided.[20–22,24,25] The diagnosis of concealed bundle of His extrasystoles should be suspected from the electrocardiogram when portions of the record demonstrate junctional extrasystoles that are conducted to the ventricle[26] or reveal second degree A-V block in a patient with a normal QRS complex.[27] The surface electrocardiogram in Case 2 demonstrated both phenomena. The sudden appearance of unexplained P-R prolongation or the occurrence of both types I and II block in the same patient is also highly suggestive of concealed His bundle extrasystoles.[21] Definite proof depends upon His bundle recording, which is a safe and useful adjunct to the surface electrocardiogram in the study and management of conduction and rhythm disturbances even in the presence of complex congenital heart disease.

Acknowledgment

We thank Miss Joyce Childress for her excellent secretarial assistance.

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Electrocardiographic Manifestations of Dual Pathways of Retrograde Impulse Conduction in the Human Heart

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Three cases are presented in which the electrocardiogram provided evidence for the functioning of two separate pathways of retrograde impulse conduction. In the first case, distinct points of entry of the impulses into the atria are inferred. In the second case, the origin of the retrograde impulses was created by the stimuli of an artificial pacemaker. In the third case, the operation of two pathways of retrograde conduction was evidenced by the demonstrated differences of the refractory periods and the conduction velocities. Each of the three cases reflects a particular aspect of the phenomenon.

Multiple atrioventricular (A-V) nodal conduction pathways with longitudinal dissociation have been invoked as the basis for certain reciprocation phenomena and for alternation of A-V conduction time.[1–7] However, except for ventricular preexcitation caused by the presence of accessory A-V pathways, evidence for the actual functioning of more than one pathway connecting the atria and the ventricles is only rarely provided by the clinical electrocardiogram. In this paper, we present findings from three patients in whom a dual pathway for retrograde conduction was strongly suggested in various settings.

Two dissociated nodal tracts can be expected either to join at the upper margin of the A-V node to form a final common pathway before entering the atria or to enter the atria at different points.[6] In the latter situation, different propagation of the retrograde impulse within the atria would be expected. The first case to be presented bears evidence for the second alternative.

Analysis of Electrocardiograms

Case 1

Figure 1: This tracing is representative of many records taken during several years of observation of a girl first seen at age 7 years. The basic dysrhythmia results from persistent sinus depression with a dominant slow junctional rhythm. Occasionally, the atria are activated by a sinus impulse, but in most instances atrial activation is anticipated by retrograde impulses emanating from the junctional pacemaker. The case exhibits two distinct types of retrograde P waves, labeled P′(1) and P′(2), which can best be appreciated by their juxtaposition in a simultaneous record of leads V_1 and II (Fig. 1).

All QRS complexes are normally shaped and are followed by an atrial deflection that exhibits one of three configurations. Those labeled N are positive in lead II. Longer strips show that the R-P intervals of these atrial deflections vary widely. Occasionally, a P wave of this type may precede the ventricular complex, and ventricular captures have been observed but are not shown. P waves of this type are of sinus origin. By contrast, P waves of the other two types—both characterized by a prominent negative deflection in lead II—are coupled to the preceding QRS complex by an R-P′ interval that varies only slightly and that characterizes each type of P′ wave (Fig. 2). The two ranges of the R-P′ intervals do not overlap. In Figure 1, type P′(1) is represented by the first three and the sixth complexes. The R-P′(1) interval

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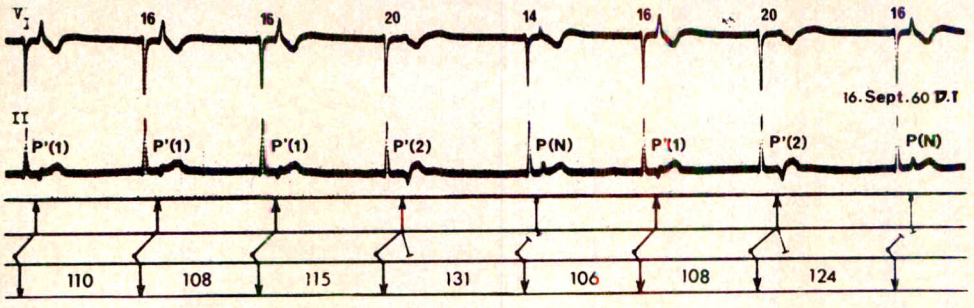


FIGURE 1. Case 1. Simultaneous recording of leads V_1 and II. Slow junctional rhythm consequent to sinus depression. (See text.)

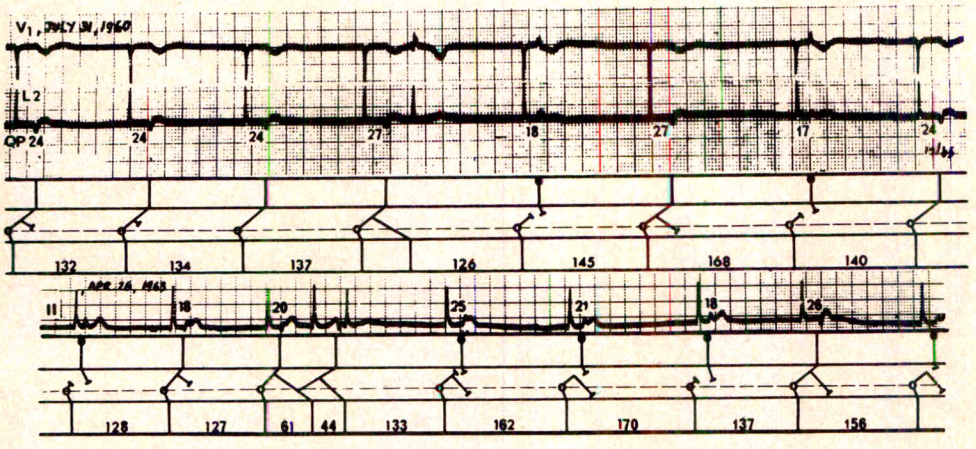


FIGURE 2. Case 1. Sinus depression, slow junctional escape rhythm with two types of retrograde conduction and with reciprocal beats. **Upper two strips:** simultaneous recording of leads V_1 and II. **Bottom strip:** Lead II recorded 3 years later. (See text.)

measures 0.16 second; the R-P′(2) value is 0.20 second. During various examinations, the range of R-P′(1) values differed slightly, but values for R-P′(2) always exceeded those for R-P′(1). In addition to the difference in the length of the R-P′ intervals, the two types of atrial deflection manifest striking differences in configuration. Thus, the P′(1) waves are characterized by a biphasic negative-positive deflection in lead II, whereas P′(2) is monophasically negative in lead II and deeper than the negative phase of P′(1). In lead V_1, P′(1) is positive and peaked, but P′(2) is low and blunt. The P′(1) wave can be distinguished from a sinus wave in lead V_1 because it is considerably taller.

It may be concluded that impulses P′(1) and P′(2), both of junctional origin, are being propagated within the atria in different directions. The different modes of intraatrial propagation of the retrograde impulses characterized by the P′(1) and P′(2) waves can be explained by one of the following hypotheses:

1. The impulses of both types enter the atria at the same point but use different intraatrial conduction pathways. The existence of specialized pathways in the atria has been described.[8] However, the assumption of retrograde impulse conduction by way of different intraatrial tracts does not account for the difference in the length of the R-P′ intervals of types 1 and 2. The latter phenomenon requires an additional hypothesis, either of two different points of origin of the junctional impulse or of two different conduction velocities below the atria. Neither of these hypotheses explains why two junctional impulses that arrive at the same point in the fully recovered atria should use different pathways for their subsequent propagation through the atria. In clinical and experimental cases in which retrograde P waves of junctional and ventricular origin appear side by side, and in cases in which the configuration of retrograde P waves generated by junctional or ventricular impulses is comparable with that of retrograde P waves generated by atrial reentry in the same case, the vectors of the P waves usually do not differ. The same similarity in P wave configuration is observed when an infraatrial impulse evokes retrograde conduction with different R-P′ intervals (see Fig. 3 and 6).[9–16] On the other hand, it has been shown that stimulation of adjacent points in the lower part of the right atrium evokes retrograde P waves with different configurations.[17]

2. It seems more probable that the impulses of types 1 and 2 start their propagation within the atria at different points of entry; it cannot be stated whether they then proceed along specialized intraatrial pathways or in a simple radial manner.

We must conclude that the impulses of the two types use two separate junctional pathways to reach the atrial level at two separate points. This conclusion rests on the combined evidence of time intervals and the shape of the retrograde P waves. The functioning of two separate conduction pathways in the A-V junction is in accord with another phenomenon that was frequently encountered in this case and that points to a longitudinal dissociation of the A-V junction, namely, several variants of reciprocal beats.

Figure 2: This tracing with its diagram serves as an interpretation of some of these variants. The upper two strips represent a simultaneous record of leads V_1 and II. The beats are of junctional origin; the fourth and the sixth beats are followed by reciprocation, the former by a manifest re-

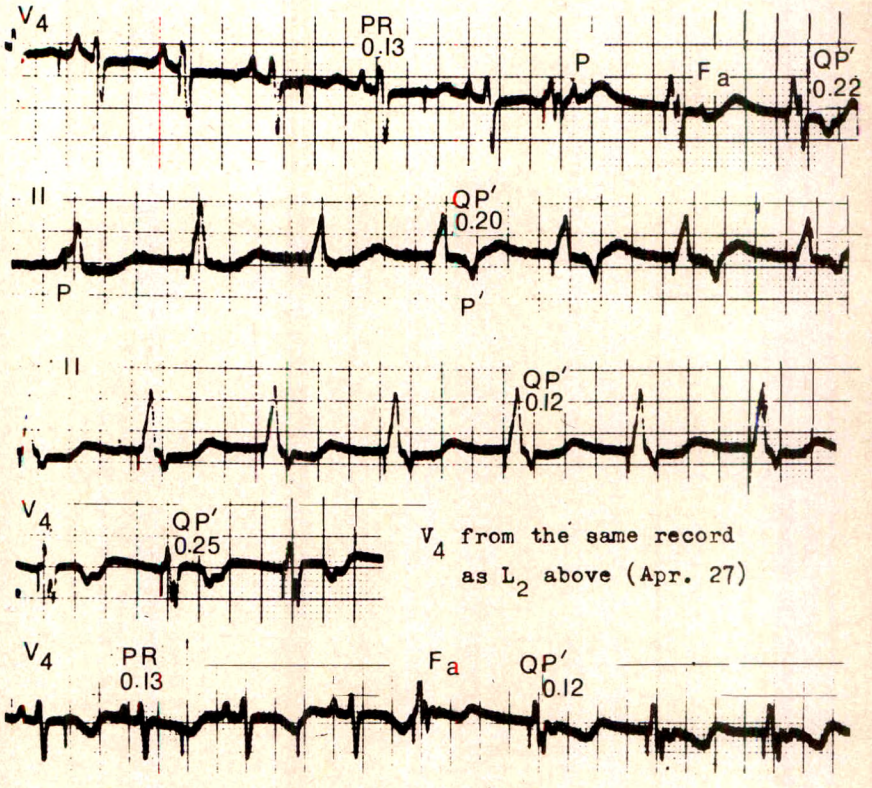


FIGURE 3. Case 2. A fixed-rate artificial pacemaker rhythm in competition with the sinus rhythm. The two **upper strips** are leads V_4 and II from the same record. The third and fourth strips are leads II and V_4 from another record. (Detailed discussion in text.)

ciprocal beat of right bundle branch block configuration and the latter by concealed reciprocation. The reflected impulse, although failing to activate the ventricles, has reached the level of the junctional pacemaker, discharged and reset it, with the consequent prolongation of the R-R interval.[10,18–20] In this sequence, the P′ waves are of type 2. It should be noted that reciprocation occurs only after relatively long R-P′ intervals; the same observation could be made in longer sequences in which the R-P′(2) interval varied within its narrow range. The bottom strip of Figure 2 represents a portion of lead II recorded 3 years later. The third beat is followed by a retrograde P wave of type 1 and initiates a double reciprocation with one atrial and two ventricular echoes.

In this case, occasional atrial beats of sinus origin prevent the reciprocation of junctional impulses if they occur relatively early (0.18 second or less) after the junctional QRS complex, but the reciprocation is protected from relatively late sinus impulses with R-P intervals of 0.21 and 0.25 second. Since the R-P′ interval measures 0.26 second (next to last complex, Fig. 2), reciprocation may occur when the antegrade atrial impulse has already penetrated the A-V node for a certain distance (bottom strip, concealed reciprocation after the fourth and fifth junctional beats). This observation, noted in several clinical cases,[10,18,21–26] favors the argument that the path for reciprocation can be completed within the A-V node, without involvement of the atria.

An unusual feature of this case is the repeated occurrence of reciprocation with both types of P′ waves although, from clinical and experimental experience, reciprocation would be anticipated only with the type characterized by the longer R-P′ intervals. If impulses of only one type are considered, the usual rule stands; only the longest R-P′ intervals within the range characteristic of the type initiates reciprocation of any variety—manifest, concealed or double. Note that reciprocal beats occurred with type 1 P′, whose longest R-P′ interval is shorter than any R-P′ interval of type 2.

In this case it has been assumed but not proved that the junctional beats all arise in the same junctional pacemaker. However, some doubt remains. In Case 2 the origin of the retrograde impulse is known with certainty, and such doubts are avoided.

Case 2

An elderly woman was examined for an illness unrelated to her heart condition, and electrocardiograms were recorded (Fig. 3). About a year earlier, a fixed-rate pacemaker had been implanted transthoracically in the left ventricle because of repeated severe attacks of Adams-Stokes seizures. At the time of the examination, the patient was free from symptoms attributable to heart disease.

Figure 3: The electrocardiogram shows the normal functioning of the artificial pacemaker, with sinus rhythm emerging whenever the sinus rate exceeds the rate of the pacemaker and the ventricles are no longer refractory after the preceding activation by the artificial pacemaker. The top strip (lead V_4) illustrates the transition from a pure sinus rhythm with a P-R interval of 0.13 second to the artificial pacemaker rhythm. This transition occurs when the sinus rhythm slows. Collision of the sinus and the artificial impulses occurs within the atria with the production of an atrial fusion beat, as seen in the next to last complex, which is between the preceding nonconducted sinus P wave and the subsequent retrograde P′ wave of the last complex. The Q-P′ interval of the last complex measures 0.22 second. The second strip presents a portion of lead II from the same record; here all the ventricular beats are artificially

induced. A sinus P wave appears shortly before the first ventricular complex; the next sinus P wave is apparently buried within the second QRS complex which, as a result, appears taller than the other QRS complexes. The third sinus P wave may be barely seen as a slight elevation on the S-T segment of the third beat and is probably a fusion beat of the sinus and the retrograde atrial activation. Beginning with the fourth ventricular beat, each QRS complex is followed at the constant interval of 0.20 second by a deeply inverted wave that cannot represent a component of the ventricular complex because it is absent in the first three beats. These inverted waves can be interpreted only as a manifestation of atrial activation by retrograde impulses emanating from the artificial pacemaker.[27,28]

The peculiar feature of the retrograde conduction in this case comes to light when the second strip is compared with the third strip. In the third strip, retrograde induced P waves follow every ventricular complex at a constant Q-P′ interval of 0.12 second, which is considerably shorter than that seen in the second strip. Since conduction in the ventriculoatrial (V-A) direction as well as in the A-V direction is influenced by many factors, such as the autonomic nervous system, perfusion of the conduction system and various drugs, it is impossible to decide on the basis of clinical tracings taken on different days whether the shortening of the Q-P′ interval is due to shifting of the retrograde impulse into a faster conducting pathway, or to one or a combination of the factors mentioned. Later during the inscription of this record, the Q-P′ interval is considerably prolonged (fourth strip), reaching a value of 0.25 second, which is more nearly comparable to that seen 2 days earlier. Although the actual shift from one Q-P′ interval to the other was not observed, its occurrence within seconds makes unlikely the possibility that a factor extrinsic to the A-V junction itself is responsible for the change. A comparison of the bottom and top strips adds further support to the assumption that the shift in Q-P′ intervals is not due to changes in conduction properties of a single A-V nodal pathway. Thus, although the P-R intervals in the two strips are the same at 0.13 second, the Q-P′ interval in the bottom strip is 0.12 second, whereas in the top strip it is 0.22 second. We therefore postulate that two distinct pathways of retrograde conduction are present in the A-V junction.

In the two cases discussed thus far, the detailed analysis of retrograde conduction was restricted because events were not observed under conditions that allow experimental alterations in the coupling intervals of premature beats. In the next case, a spontaneously occurring complex arrhythmia created conditions that approximate those of such an experiment.

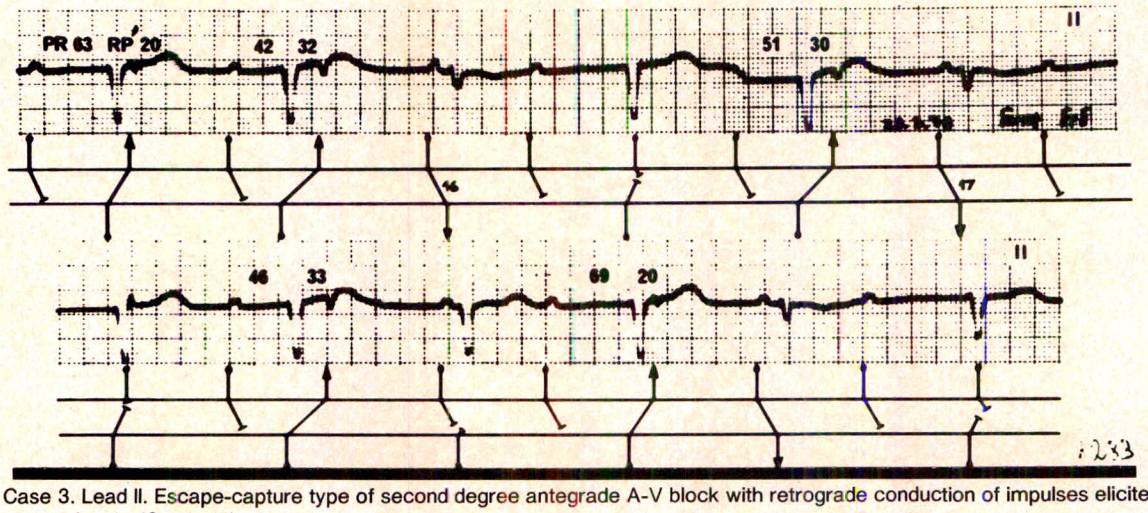
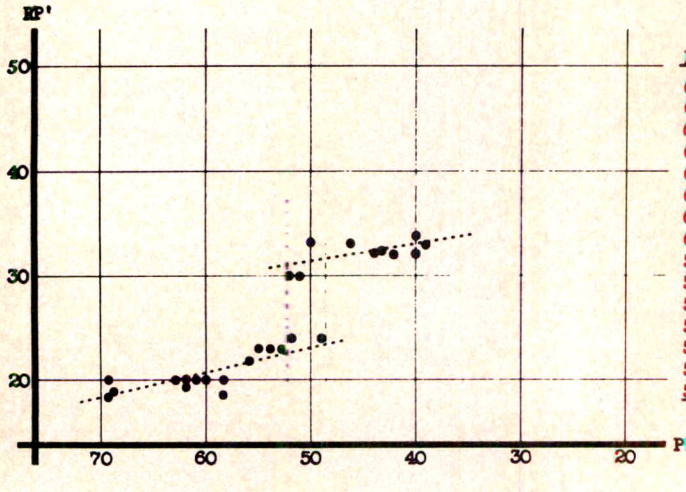


FIGURE 4. Case 3. Lead II. Escape-capture type of second degree antegrade A-V block with retrograde conduction of impulses elicited by some ventricular escape beats. (See text.)



PR	RP'	PR	RP'
69	18	52	30
69	18	51	30
69	20	50	33
63	20	49	24
62	19	46	33
62	20	44	32
61	20	44	32
60	20	42	32
58	18	40	32
58	20	40	34
56	22	39	33
55	23		
54	23		
53	23		
52	24		

FIGURE 5. Case 3. Table and chart exhibiting the inverse relation between the P-R and R-P′ intervals. (See text.)

Case 3

Figure 4: This tracing (lead II) is that of a 73 year old man with severe atherosclerotic heart disease. As shown in the diagram, second degree A-V block is present. When the sinus impulse is blocked, escape beats appear, probably of infranodal origin. The escape-capture pattern is further modified by retrograde impulses that emanate from the escape beats; they exhibit the known phenomenon of unimpaired retrograde conduction in the face of antegrade A-V block.[29–35] The combined presence of functioning retrograde conduction in the face of advanced second degree antegrade block, a normal P-R interval of the conducted beats and the complete left bundle branch block suggest that bilateral bundle branch block is the mechanism of the advanced A-V block. The atrial discharges of sinus origin are not synchronized with the ventricular escape beats; the latter occur at variable intervals after the preceding sinus P wave. Descending sinus impulses (right of center, top strip; left of center, bottom strip) interfere with some of the retrograde impulses that issue from the escape beats. Other retrograde impulses reach and discharge the sinus node, shifting its discharge sequence. Because of the lack of synchronization, the retrograde impulses traverse the A-V junctional tissues in various stages of the relative refractoriness caused by the immediately preceding descent of a blocked sinus impulse.[36]

Figure 5: As anticipated, the V-A conduction time proves to be inversely related to the interval between the preceding sinus P wave and the escape beat. The available values of the P-R interval and the corresponding R-P′ interval are tabulated and plotted in Figure 5. As escape beats shift from 0.70 to about 0.50 second after the preceding sinus P wave, the subsequent retrograde conduction time R-P′ increases linearly. However, at the critical juncture of about 0.52 second, the smooth regression line is suddenly broken. With the further decrease of P-R*, the values of R-P′ jump to a higher level and then continue to increase linearly along a line that is roughly parallel to the first. In a narrow transition range of P-R* values, indicated in the diagram by the vertical broken lines, the retrograde impulses can be conducted with either long or short R-P′ intervals.

The sudden increase in the conduction time suggests that retrograde conduction switches from one pathway to another.[1,3–5,9] It is assumed that one of the pathways is endowed with a shorter conduction time and a longer refractory period than the other[1,4–6,9] (beta and alpha pathways, respectively).[5,9] As long as the coupling time of the retrograde ventricular impulse with respect to the preceding blocked P wave exceeds the refractory period of both pathways, the impulse is transmitted by both routes but reaches the atria (or an upper common pathway) only by the pathway with the faster conduction. The resulting refractoriness of the atria (or an upper common pathway) prevents the activation of the atria by the impulse that has entered the alternative route. This fact accounts for the left part of the graph (Fig. 5).

Further shortening of the P-R interval, however, brings the start of retrograde conduction into the range of the long refractory period of the pathway with the faster conduction; the impulse is now blocked in this pathway, thus allowing the pathway with the shorter refractory period and the slower conduction to become operative. In this case, the existence of two separate conduction pathways is inferred from observations that delineate two different sets of conduction properties.

Comment

Evidence for the existence of dual A-V junctional pathways of retrograde conduction in the human heart has been adduced by analysis of conventional electrocardiograms. The concept of a functional dissociation of the two pathways is fundamental for the understanding of various electrophysiologic phenomena. The extrapolation of laboratory findings to conditions in the diseased human heart cannot be taken for granted and must be validated by clinical observations, some of which manifest themselves only under exceptional conditions. Measurement of the H′-A′ interval in cases such as these would be of great interest. However, rare and evanescent events remain the realm of routine surface electrocardiography, which holds its place as an indispensable research tool for the detection and interpretation of spontaneously occurring conduction variants.

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* P-R here denotes the distance between a nonconducted atrial impulse and a ventricular escape beat.

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Conduction System in Systemic Lupus Erythematosus with Atrioventricular Block

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We describe the clinical course and the postmortem cardiac findings in a 12 year old girl with systemic lupus erythematosus, complete heart block, renal failure and hyperkalemia. The conduction system was examined by serial section. The sinoatrial and atrioventricular nodes were found to be almost completely replaced by granulation tissue; we believe that this finding is related to the systemic lupus. The hyperkalemia is not considered to be the cause of the block, since the block persisted despite the lowering of the blood potassium level and the morphologic findings in this case are not found in hyperkalemia.

Systemic lupus erythematosus in association with complete heart block[1–5] occurs rarely and has only occasionally been subjected to conduction system studies.[1] We recently studied, clinically and with serial sections of the conduction system, a case of systemic lupus erythematosus with atrioventricular (A-V) block.

Clinical Review

A 12 year old black girl was well until November 9, 1972, when she returned from school with fever, chills and easy fatigability. The next day swelling of the legs and pink urine were noted, and she was admitted to a suburban community hospital.

Physical examination on admission revealed an afebrile patient with a blood pressure of 140/100 mm Hg. The eyes were puffy and there was generalized edema. Chest roentgenograms and an electrocardiogram were normal. Blood count and chemistry determinations were: hemoglobin 10.3 g/100 ml, hematocrit 33 percent, creatinine 2.8 mg/100 ml and potassium 6.3 mEq/liter. Urinalysis revealed cloudy urine with 300 mg/100 ml of albumin, 50 to 70 red blood cells and 50 to 60 white blood cells per high power field, few coarse granular casts and 1 to 3 finely granular casts. Blood cultures were sterile, and throat cultures did not grow out beta hemolytic streptococci. The antistreptolysin titer was 333 units. During the course of the patient's hospital stay there was a progressive increase in blood urea nitrogen from 58 to 95 mg/100 ml and the creatinine level rose to 4.2 mg/100 ml. Serum potassium values ranged from 4.2 to 5 mEq/liter. A 24 hour urinary specimen on November 23 contained 9.6 g of albumin. Results of a lupus erythematosus preparation were positive on three occasions as were the results of the antinuclear test for systemic lupus erythematosus. On November 24 the patient was transferred to La Rabida Hospital.

Physical examination on admission disclosed a temperature of 40.3° C, pulse rate of 128/min and blood pressure of 180/110 mm Hg. The heart was not enlarged and the heart sounds were normal. No murmur or pericardial friction rub was noted. There was bilateral pitting ankle edema.

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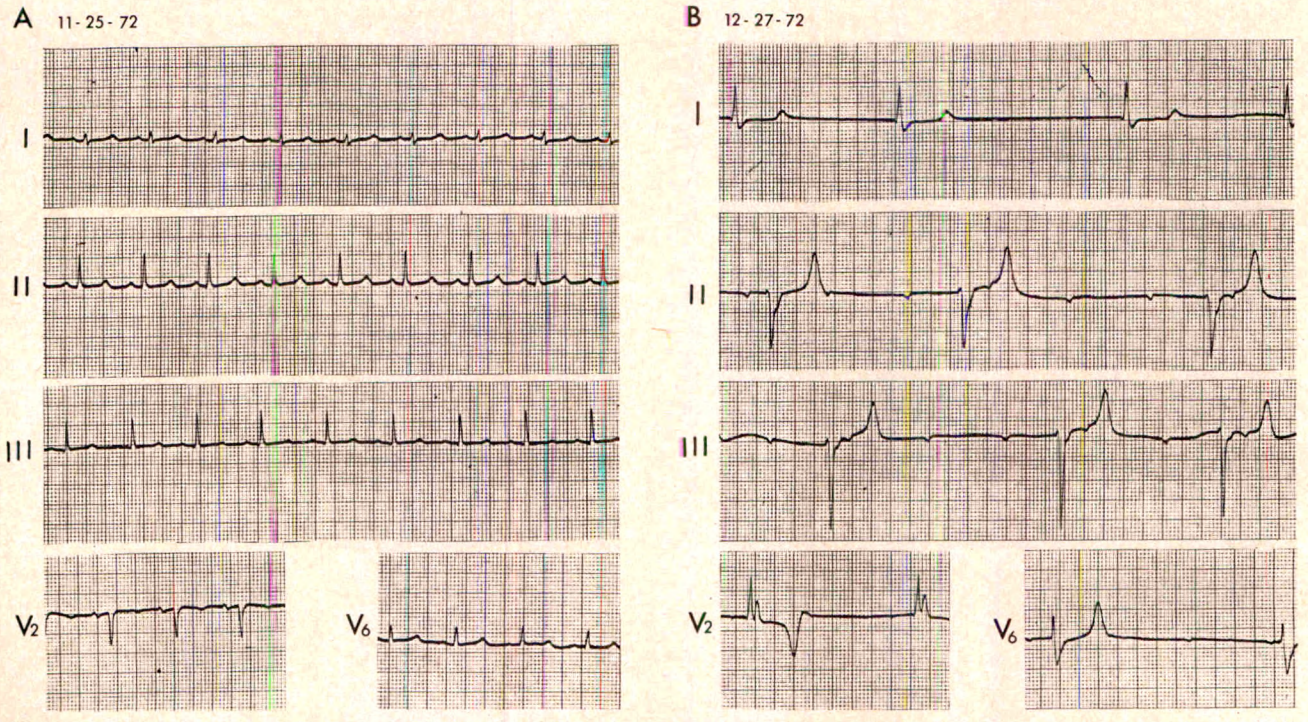

FIGURE 1. Electrocardiograms. **A,** November 25, 1972, revealing normal sinus rhythm, normal QRS axis and normal intraventricular conduction. Findings on subsequent serial tracings were essentially the same until December 27, 1972 (**B**), when the tracing demonstrated complete A-V block with an ectopic low atrial (or junctional) pacemaker at a rate of 75/min, a ventricular rate of 30/min, wide QRS complexes with a duration of 0.16 second, a pattern of right bundle branch block and an axis of −60°.

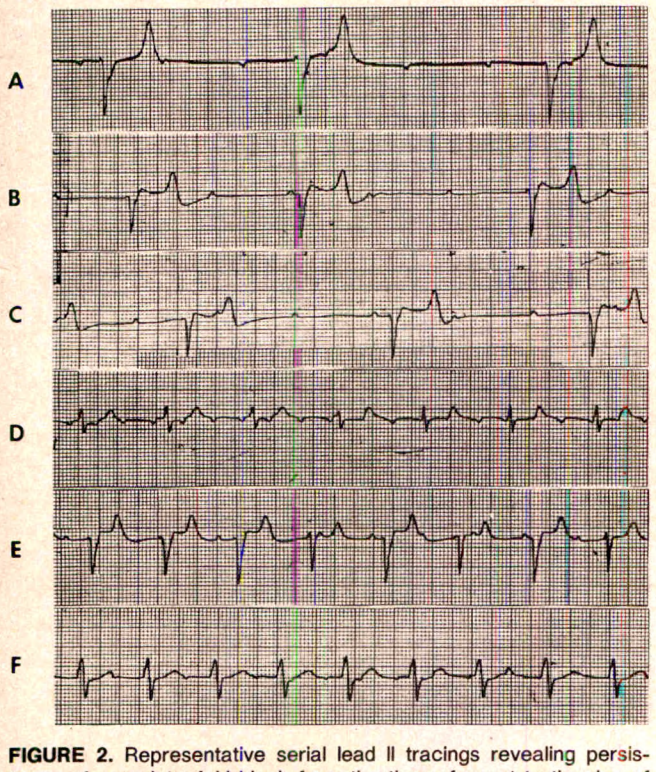

FIGURE 2. Representative serial lead II tracings revealing persistence of complete A-V block from the time of onset to the day of death 3 days later (**A to F**); spontaneous shift in atrial pacemaker minutes after the onset of the arrhythmia (**B**); no significant change after a decrease in serum potassium from 7.1 to 5.3 mEq/liter (**C**); the effects of isoproterenol infusion on heart rate, QRS duration and axis (**D**); changes in P waves, QRS duration and axis 12 and 20 hours after discontinuation of isoproterenol infusion (**E and F,** respectively).

Hospital Course

The patient was treated for renal failure with repeated peritoneal dialysis, and was given the following drugs: prednisone, 25 mg every 6 hours (on December 2 through 8, 11 through 13 and 19 through 26); Solu-cortef®, 100 mg intravenously every 6 hours (on December 9 through 10 and 17 through 18), and 60 mg intravenously every 6 hours (on December 27 through 30); Aldomet®; Valium®; phenobarbital; and methicillin sodium. Results of a renal biopsy on December 5 were consistent with severe extracapillary and endocapillary proliferative lupus glomerulonephritis. Serial electrocardiograms on November 25 and 28 and December 4 and 8 revealed normal sinus rhythm and normal intraventricular conduction, that is normal QRS complexes (Fig. 1A). Serum potassium levels ranged from 2.8 to 7.1 mEq/liter during this period. The pulse rate was normal until December 27 when, at the start of the fourth peritoneal dialysis, the heart rate suddenly slowed to 32 to 36 beats/min. Other vital signs were normal and the patient otherwise showed no other pertinent abnormality. An electrocardiogram recorded at that time (Fig. 1B) revealed complete A-V block with an ectopic low atrial (or junctional) pacemaker at a rate of 75/min; a ventricular rate of 30/min, wide QRS complexes with a duration of 0.16 second and a pattern of right bundle branch block and left axis deviation. A chest X-ray film disclosed an enlarged cardiac silhouette. A repeat lead II electrocardiogram taken several minutes after the first revealed upright P waves, indicating a spontaneous shift in the pacemaker governing the atria from low atrial (or junctional) to sinus (Fig. 2B). The potassium level at this time was 7.0 mEq/liter, blood urea nitrogen 268 mg/100 ml and creatinine level 21 mg/100 ml. The potassium level was reduced to 5.3 mEq/liter 2 1/2 hours after peritoneal dialysis. However, complete A-V block with slow ventricular rate persisted with no change in the electrocar-

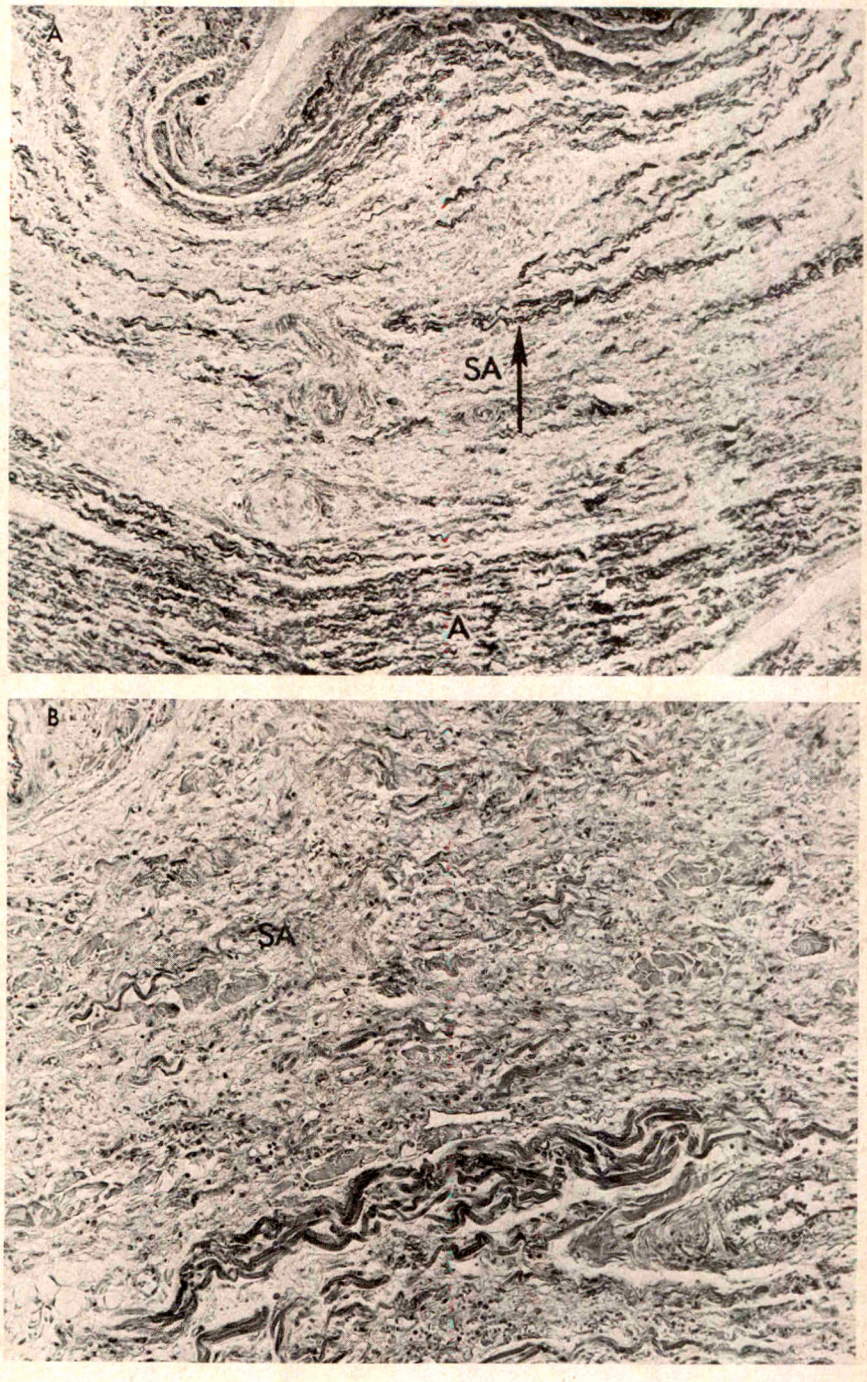

FIGURE 3. Sinoatrial (S-A) node. **Arrow** points to remainder of S-A nodal fibers. Gomori Trichrome stain × 45 **(A)** and hematoxylin-eosin stain × 150 **(B),** reduced by 25 percent. A = atrium.

diographic pattern (Fig. 2C). Intravenous infusion of isoproterenol was started, the dose ranging from 0.2 to 0.8 μg/min. The ventricular rate then increased to 60 to 80/min, the QRS duration decreased to 0.08 second and the QRS axis manifested less deviation to the left but the complete A-V block persisted (Fig. 2D). The pacemaker governing the atria shifted to a low atrial (or junctional) site with a rate of 170 to 200/min. This increase in rate could have reflected abolition of exit block of the previously described low atrial rhythm (Fig. 2A). Administration of isoproterenol was discontinued on December 29. Within the next 20 hours, serial electrocardiograms (Fig. 2, E and F) revealed increased QRS duration of 0.12 second, variations in the degree of leftward deviation of the QRS axis, shifts in the pacemaker governing the atria between sinus and ectopic low atrial (or junctional) focus, slowing of the atrial rate and persistence of complete A-V block, but the ventricular rate remained unchanged at 60 to 90/min. Serum levels at this time were: potassium 4.5 mEq/liter, blood urea nitrogen 92 mg 100 ml and creatinine 11 mg/100 ml. Transfer of the patient to another hospital for transvenous pacemaker insertion was considered, but her condition was semimoribund and she died suddenly on December 30, 1972.

Autopsy Findings

Aside from the findings in the heart, the pathologic diagnoses were: (1) systemic lupus erythematosus with lupus

nephritis and renal failure; (2) pulmonary edema with acute necrotizing bronchopneumonia; and (3) acute hemorrhagic gastritis and colitis. On gross examination, the heart weighed 279 g. All the chambers were hypertrophied and enlarged. The valves showed no endocarditis.

Histologic Examination

Methods: The sinoatrial (S-A) and A-V nodes and their approaches, the A-V bundle and the bundle branches up to the level of the moderator band were serially sectioned and every 10th section was retained. The atrial preferential tracts were serially sectioned and every 20th section was retained. The remainder of the heart was divided into blocks and two sections were taken from each block. Sections of the S-A node, the A-V node, the A-V bundle and the beginning of the bundle branches were successively stained with hematoxylin-eosin, Weigert-Van Gieson and Gomori trichrome stains. The remainder of the sections were alternately stained with hematoxylin-eosin and Weigert-Van Gieson stains. Altogether, 914 sections were examined. Data from previous studies[6,7] on the conduction system in patients in the same age group as our patient were used as control measurements.

Conduction system: *S-A node:* This was mostly replaced (Fig. 3), especially the periphery, by fibroblastic and mononuclear cells with degenerative changes present in the remaining cells. The arteries and arterioles manifested swelling of the medial muscle cells with proliferation of young connective tissue in the adventitia.

Approaches to the S-A node: The vessels showed changes similar to those described in the S-A node (Fig. 4). Many atrial cells had acute degenerative changes.

Approaches to the A-V node: There was moderate irregular degeneration of the cells with vascular changes as described for the S-A node.

A-V node: Almost the entire A-V node was replaced by granulation tissue (Fig. 5), and degenerative and early necrotic changes of small vessels and capillaries were evident.

A-V bundle, penetrating portion: There was considerable proliferation of young connective tissue with a slight infiltration of mononuclear cells.

A-V bundle, branching: There was a slight proliferation of young connective tissue.

Left bundle branch: The main bundle showed a slight proliferation of young connective tissue with a slight infiltration of mononuclear cells and eosinophils. The periphery showed no abnormalities.

Right bundle branch: Slight infiltration with mononuclear cells and slight acute degenerative changes were found.

Atrial preferential pathways: Considerable vascular changes with focal necrosis were present.

Myocardium: The myocardium was the seat of marked vascular changes, with moderate focal necrosis, especially in the left ventricle and septum.

Discussion

Our patient had lupus nephritis with generalized vascular disease and terminal uremia. The morphologic origin of the A-V block appears to have been the replacement of the A-V node and the beginning of the penetrating portion of the A-V bundle by young connective tissue infiltrated by mononuclear cells. A similar process had also involved the S-A node. These changes are probably related to the associated vasculitis of systemic lupus erythematosus.

Role of hyperkalemia in A-V block: The serum potassium level was elevated at the time complete A-V block developed. It is well known that hyperkalemia can induce profound changes in cardiac automaticity and conduction, and experimental studies have shown that potassium-induced conduction block may occur proximal or distal to the main His bundle.[8] The question therefore arises whether hy-

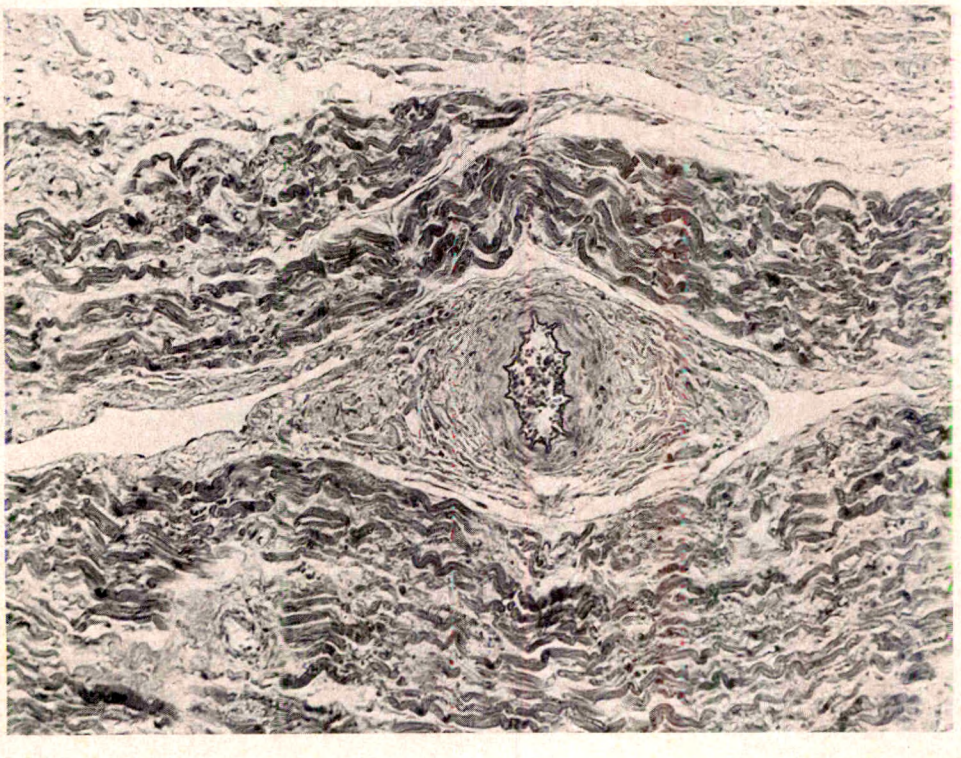

FIGURE 4. Approaches to S-A node, manifesting vascular changes. Hematoxylin-eosin stain ×150, reduced by 15 percent.

perkalemia had a role in the electrocardiographic changes observed in this case.

We believe that it did not play a primary role. The serum potassium level at which grossly evident depression of conduction occurs is usually greater than 8 mEq/liter[9]; our patient had a level of only 7 mEq/liter. It is possible that in the presence of severe disease this level might be sufficient to produce conduction block, but our patient had previously had serum potassium levels of up to 7.1 mEq/liter without detectable impairment in A-V conduction. Furthermore, there was no significant change in the electrocardiogram after the reduction in serum potassium to normal values. The shifts in the pacemaker site governing the atria between the sinus node and an ectopic low atrial (or junctional) focus also were not correlated with the serum potassium level. These facts indicate that some factor other than hyperkalemia was responsible for the electrical changes.

Morphologic basis for the A-V block: Morphologic data are consistent with this evaluation. There are no reported morphologic studies to indicate that hyperkalemia causes replacement of the A-V node by young connective tissue. However, necrotizing arteritis and collagen changes have been described as producing focal degeneration and fibrosis of the S-A node, and focal degeneration and inflammatory changes in the A-V node in systemic lupus erythematosus.[1] Therefore the marked degenerative and inflammatory changes in the S-A and A-V nodes, the penetrating portion of the A-V bundle, and the atrial and ventricular myocardium in our case are probably related to the systemic lupus and are responsible for the A-V block and the shifting atrial pacemaker. The hyperkalemia could have been an aggravating factor but was not critical in the functional alteration in conduction.

Role of corticosteroid therapy: We do not believe that corticosteroids were responsible for the vascular and parenchymatous changes. Although these changes have been described after long-term corticosteroid treatment in rheumatoid arthritis,[10–12] the duration of treatment with corticosteroids was very short in our case. If the granulation tissue in the S-A and A-V nodes is the result of healing from previous necrosis and vascular changes produced by these compounds then these changes would have had to occur after the onset of corticosteroid treatment.

Response to isoproterenol: Further clinicopathologic correlation can be inferred if the response to isoproterenol is viewed in the light of the histologic findings. Isoproterenol, like other catecholamines, has been known to improve responsiveness and conduction in partially depressed cardiac fibers although the precise mechanism of action remains unclear.[13–16] The severity of the lesion in the A-V node could explain the failure of isoproterenol to restore conduction across the A-V junction, and the relatively less

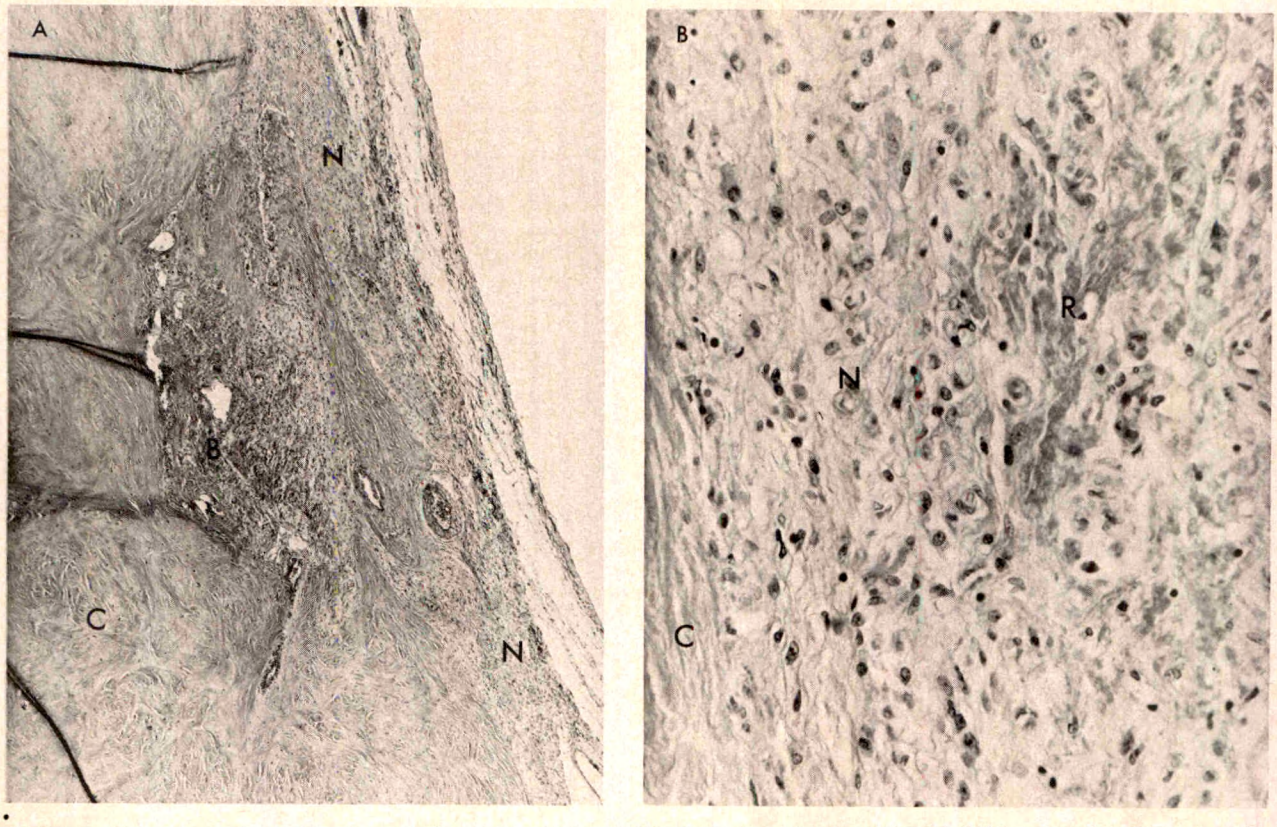

FIGURE 5. A, A-V node and beginning of penetrating portion of the bundle of His; hematoxylin-eosin stain ×45, reduced by 31 percent. **B,** A-V node; hematoxylin-eosin stain ×375, reduced by 29 percent. B = bundle of His; C = central fibrous body; N = A-V node; R = remnants of nodal cells.

severe degree of involvement of the bundle branches and distal conduction system could account for the improvement in intraventricular conduction, as reflected by the narrowing of the QRS complexes, in the presence of isoproterenol.

Conduction defects in lupus: A review of the reported cases of systemic lupus erythematosus with A-V block reveals that the block may be a terminal event,[1,3] as in our case, and may be due to changes in the A-V node.[1] However, it may be preceded by bundle branch block[2] and in such cases the A-V block may be due to bilateral bundle branch block.[2] The patient in one such case was alive, with an artificial pacemaker, at the time the report was published. When vascular changes dominate the findings, there appears to be a predilection for destructive changes in the S-A and A-V nodes.[1]

Atrioventricular block may occur as a complication of other collagen diseases such as dermatomyositis,[17] polyarteritis[18] and scleroderma.[19–22] From clinical and morphologic studies, it appears that the block in any of these diseases, as in systemic lupus erythematosus, may lie proximal or distal to the A-V bundle.

Acknowledgment

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Systemic Lupus Erythematosus as a Cause of Severe Mitral Regurgitation

New Problem in an Old Disease

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Clinical and morphologic observations in three patients with systemic lupus erythematosus and severe mitral regurgitation are described. Attention is called to the "healing" of Libman-Sacks endocarditis, an infrequent occurrence in patients with systemic lupus erythematosus in the era before steroid therapy. The mitral regurgitation in our patients appears to have resulted from "healing" of the Libman-Sacks vegetations by scarring and calcification. The healing is attributed to long-term corticosteroid therapy.

For nearly 50 years, it has been known that systemic lupus erythematosus may affect cardiac valves. The lesions, however, have rarely been reported to cause valvular dysfunction[1–4] and, consequently, the diagnosis of Libman-Sacks endocarditis has been established almost exclusively at necropsy. With the advent of corticosteroid therapy the clinical findings in systemic lupus erythematosus changed.[5] Longevity increased, the endocardial verrucae often healed and valvular dysfunction became apparent. This report describes clinical and cardiac morphologic observations in three patients with severe mitral regurgitation associated with systemic lupus erythematosus. Each had received corticosteroid therapy for long periods.

Patients Studied

Clinical findings: Pertinent clinical and morphologic data in the three patients are summarized in Table I. Systemic lupus erythematosus had been present in each for 4 years or longer. Each patient had received more than 40 mg of prednisone daily for more than 1 year. Patients 1 and 3 had systemic hypertension and one (Patient 3), steroid-induced diabetes mellitus. All three had loud (grade 3–4/6 intensity) precordial systolic murmurs. Diagnosis of mitral regurgitation in each was made many months before the onset of congestive heart failure, which caused death in Patients 1 and 2 (Fig. 1) and necessitated mitral valve replacement in Patient 3.

Pathologic findings: Morphologic cardiac findings in the three patients were similar (Fig. 2 and 3). The hearts were enlarged (the two examined at necropsy weighed 600 and 450 g, respectively). The pericardial spaces were obliterated by fibrous adhesions. The mitral valve leaflets and chordae tendineae were diffusely thickened. The posterior leaflets and their chordae tendineae adhered to the underlying left ventricular mural endocardium by means of dense fibrous tissue. The anterior mitral leaflets were diffusely scarred but were free of inflammatory cells and calcific deposits. The posterior leaflets and the material behind them consisted of vascularized fibrous tissue containing collections of lymphocytes, plasma cells and calcific deposits. Hematoxylin bodies, Aschoff bodies and stainable organisms were absent in the hearts of all three patients.

Sections of lung in each of the three patients disclosed medial hypertrophy and cellular intimal proliferation of many muscular pulmonary arteries, severe intimal proliferation of many pulmonary veins, focal thickening of alveolar septae by fibrous tissue, cuboidalization of alveolar lining cells and collections of erythrocytes and hemosiderin-laden macrophages in many alveoli. These changes are characteristic of chronic congestive cardiac failure with pulmonary venous hypertension.

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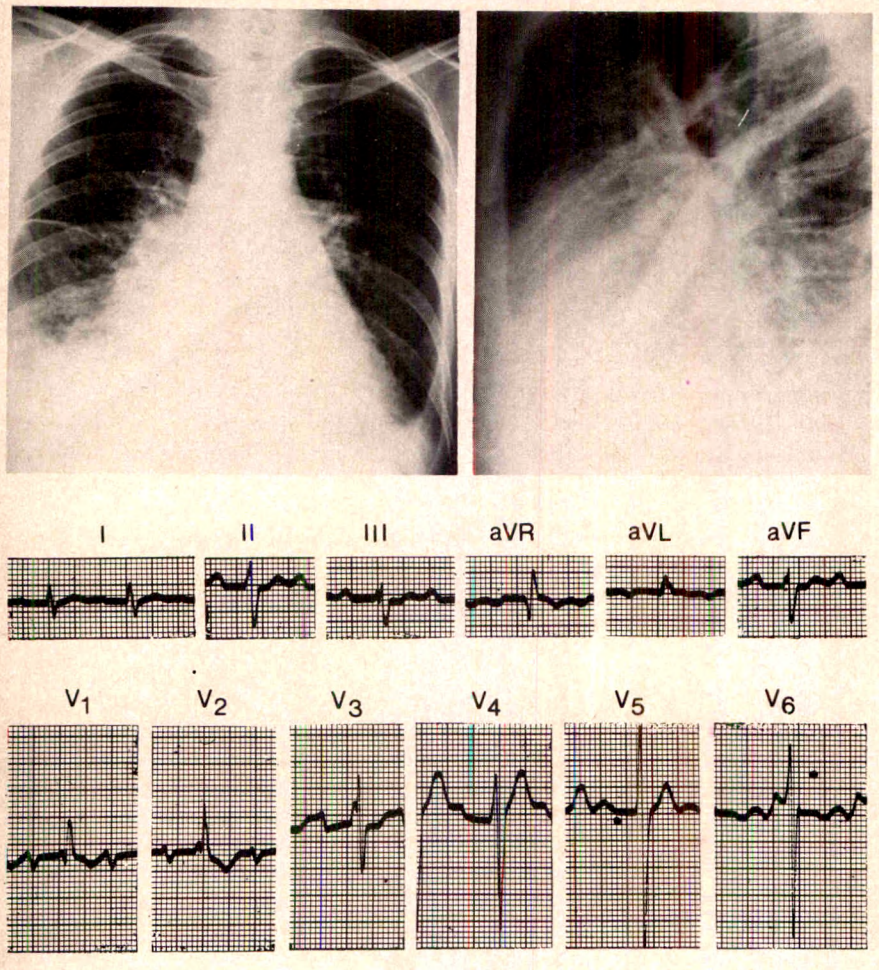

FIGURE 1. Case 1. Chest roentgenograms and electrocardiogram taken 2 weeks before death.

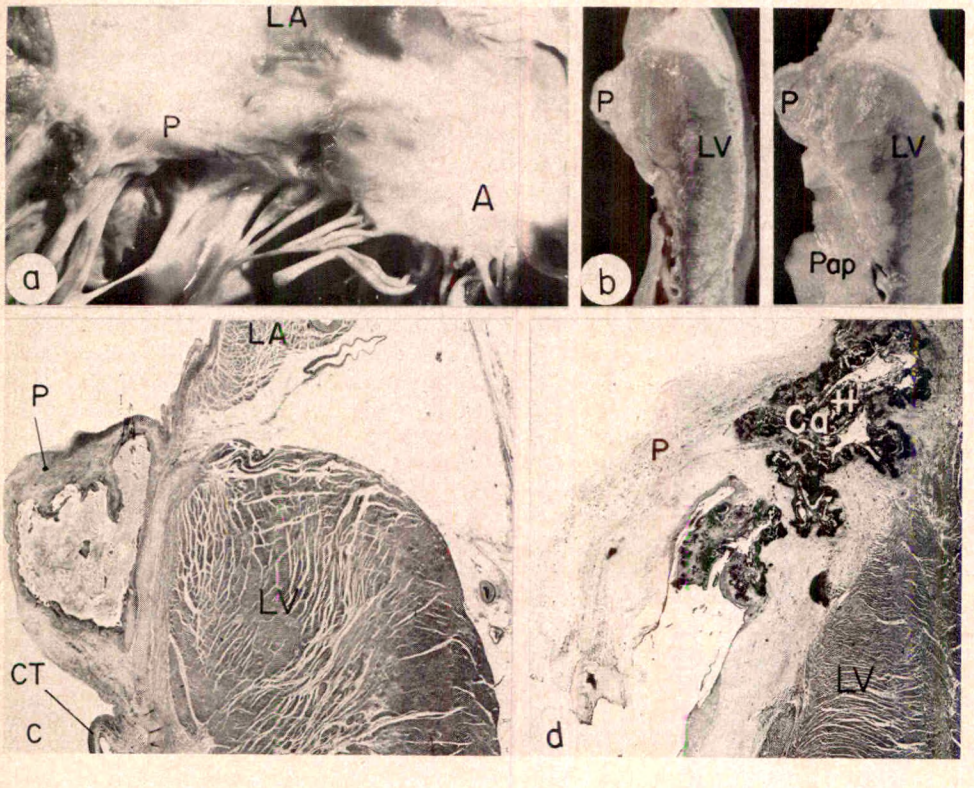

FIGURE 2. Case 1. Healed Libman-Sacks endocarditis. **a,** opened left atrium (LA), mitral valve and left ventricle. The anterior (A) and posterior (P) valvular leaflets and their chordae tendineae are diffusely thickened. **b,** longitudinal sections, including walls, of left atrium, left ventricle (LV) and posterior (P) mitral valve leaflet; the leaflet is adherent to the underlying mural endocardium. **c** and **d,** histologic sections, including posterior (P) mitral valve leaflet. Calcific deposits (Ca^{++}) are present in the posterior leaflet. The underlying mural endocardium is thick. CT = chordae tendineae; Pap = papillary muscle. Movat stain ×2 **(c),** hematoxylin-eosin stain ×5 **(d),** both reduced by 30 percent.

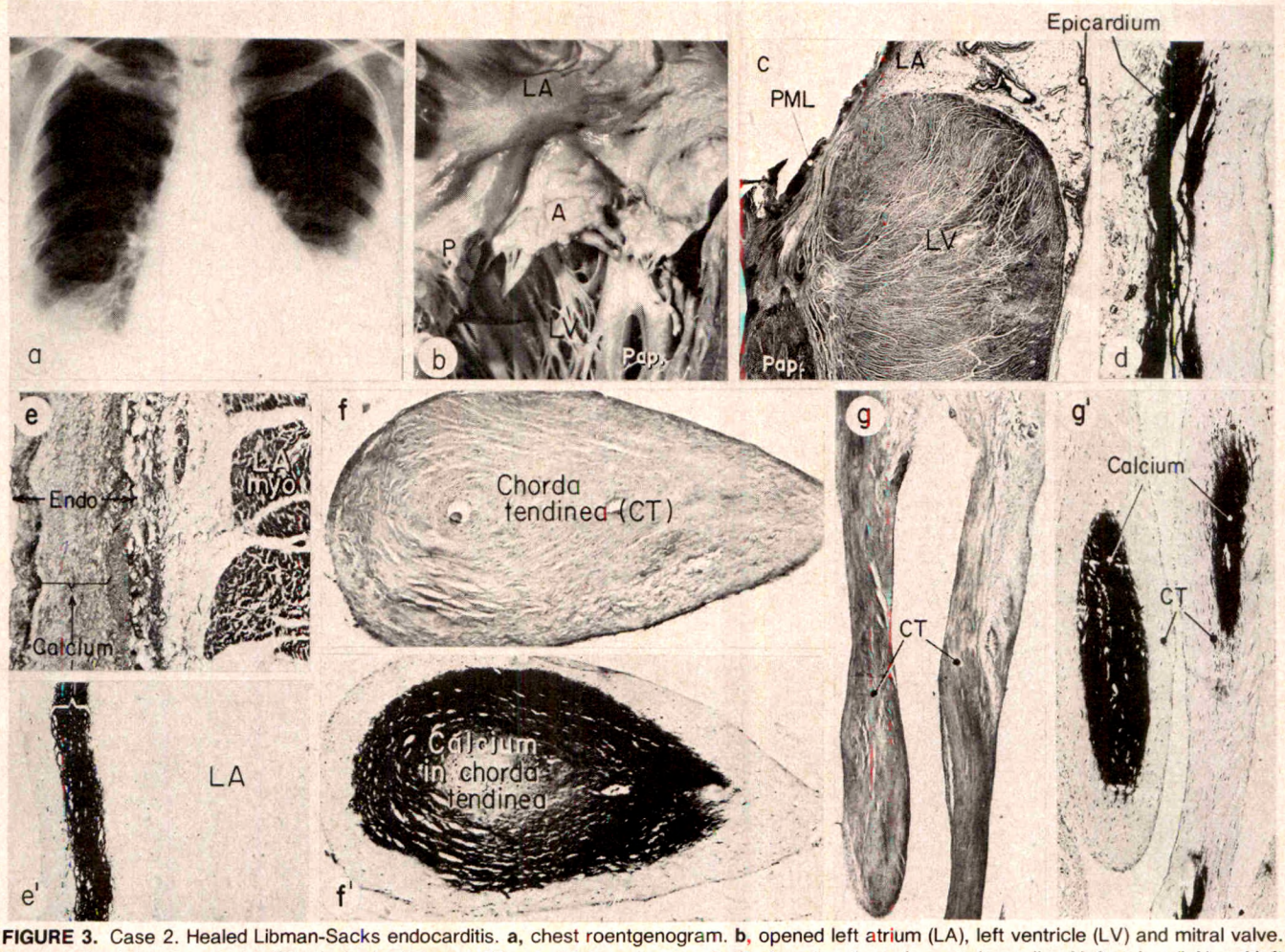

FIGURE 3. Case 2. Healed Libman-Sacks endocarditis. **a,** chest roentgenogram. **b,** opened left atrium (LA), left ventricle (LV) and mitral valve. The anterior (A) and posterior (P) valvular leaflets are diffusely thickened. **c,** longitudinal section through posterior walls of left atrium (LA) and left ventricle (LV) including portions of posteromedial papillary muscle (pap.) and posterior mitral valve leaflet (PML). The latter is fused to left ventricular mural endocardium (myo). **d,** calcific deposits (stained black) are present within the epicardium, which is thickened by fibrous tissue. Similar calcific deposits are present in left atrial endocardium (Endo) (**e** and **e**^{1}), and in chordae tendineae (CT) (**f, f**^{1}, **g, g**^{1}). Hematoxylin-eosin stains (**c, e, f, g**), Von Kossa stains (**d, e**^{1}, **f**^{1}, **g**^{1}); × 3 (**c**), × 68 (**d, e, e**^{1}, **f, f**^{1}), × 50 (**g, g**^{1}), reduced by 44 percent.

Comments

In patients with systemic lupus erythematosus described before steroid therapy was available, the endocarditis rarely caused valvular dysfunction.[1–4] The verrucae were located primarily on the undersurfaces of the mitral and tricuspid valve leaflets and on adjacent ventricular mural endocardium ("pocket" lesions). Thus, the surfaces of the leaflets over which blood flowed remained smooth, and precordial murmurs were rarely produced. The verrucae rarely "healed"[3] and never calcified.

Although the mitral lesions in each of our three patients were also located primarily on the undersurfaces of the posterior leaflets, in other respects the lesions were quite different. Few fresh lesions were present. The posterior leaflets and their chordae tendineae were firmly bound to the underlying mural endocardium by dense fibrous tissue containing plasma cells and calcific deposits; the anterior leaflets were diffusely scarred. The valvular and subvalvular scarring and calcification produced severe mitral regurgitation in each patient, resulting in severe congestive heart failure that was fatal in two and required mitral valve replacement in the third.

The healing of the verrucae appears to have been responsible for the severe valvular dysfunction in our three patients. Although loosely adhering the posteri-

TABLE I

Mitral Regurgitation Secondary to Systemic Lupus Erythematosus

Case no.	Age (yr) & Sex	Duration (mo) SLE	Steroid Therapy	Pre-cordial Murmur	CHF	ECG
1	32M	72	60	38	10	RBBB
2	45F	63	12	41	22	LAD
3	18F	48	45	48	2*	LVH

* Before valve replacement.

CHF = congestive heart failure; ECG = electrocardiogram; LAD = left axis deviation; LVH = left ventricular hypertrophy; RBBB = right bundle branch block; SLE = systemic lupus erythematosus.

or left ventricular walls to the adjacent posterior mitral valve leaflets and chordae, the soft friable "active lesions" described by Libman and Sacks[1] do not appear capable of restricting leaflet excursion or papillary muscle motion. Healing of the active lesions, however, may produce dense fibrous tissue and calcific deposits that may rigidly fuse the posterior mitral leaflet, chordae and papillary muscle to the posterior left ventricular wall. Thus, the "healing" of Libman-Sacks endocarditis may lead to severe restriction of valvular movement in a manner somewhat analogous to the development of constrictive pericarditis after healing of certain types of acute pericarditis. Corticosteroids appear to play a major role in healing the active Libman-Sacks lesions. It is likely that these drugs act directly on the active lesions, but possibly their effect is simply to increase longevity; the additional time may thus allow the lesions to heal "naturally."

Calcification of the mitral annular region appears to be accelerated by systemic hypertension and diabetes mellitus,[6] both of which may be aggravated or induced by corticosteroid therapy. Hence, the side effects of corticosteroid treatment may also accelerate the occurrence of calcific deposits in the mitral "pocket." Of our three patients, calcific deposits were most extensive in the one (Patient 3) with both hypertension and steroid-induced diabetes mellitus and least extensive in the one with neither associated condition.

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Myocardial Infarction Due to Coronary Atherosclerosis in Three Young Adults with Systemic Lupus Erythematosus

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Three patients, 24, 24 and 25 years of age, with systemic lupus erythematosus had signs of myocardial infarction. Two had serial electrocardiographic changes indicative of infarction without any cardiac symptoms. The third patient had clinical evidence of an acute massive myocardial infarction, which was proved at autopsy to be due to coronary atherosclerosis. This case is presented in detail and the association between systemic lupus erythematosus and myocardial infarction is reviewed. It is postulated that the relation between lupus erythematosus and coronary atherosclerosis is more than coincidental.

Myocardial infarction is seen infrequently in patients with systemic lupus erythematosus and there has been some controversy concerning the relation between lupus erythematosus and coronary atherosclerosis.[1–3] In 1 year we observed three young adults with systemic lupus erythematosus and signs of coronary artery disease. The first patient, a 25 year old woman, was admitted with an acute myocardial infarction complicated by cardiogenic shock; she died and on autopsy had evidence of coronary atherosclerosis as the cause of the infarction. The other two patients, both 24 years of age, had only classic electrocardiographic changes indicative of myocardial infarction and no symptoms referable to the heart.

Case Reports

Case 1. A 25 year old woman was admitted to Mount Sinai Hospital because of chest pain of six days' duration. Twelve years earlier she had choreiform movements that lasted several weeks but responded to treatment with corticosteroids. Four years later she again had episodes of chorea, this time accompanied by pain in the hips and elbows. On admission to another hospital where lupus erythematosus preparations were reportedly positive, she was treated with prednisone, 75 mg daily; this dose was gradually decreased. The choreiform movements, especially of the hands and tongue, recurred frequently, always responding to reinstitution of large doses of corticosteroids. While receiving steroid therapy she was noted to have hypertension but was not treated for it.

Six months before admission she was hospitalized because of arthralgia and pleuritic chest pain. A chest roentgenogram and an electrocardiogram were reported to be normal. The amount of prednisone administered was increased and the pains disappeared; 3 months later she was asymptomatic and prednisone was administered in gradually reduced doses and then discontinued.

Two weeks before admission she had an episode of severe chest pain precipitated by exertion and relieved by resting. This pain was substernal without radiation and made worse by deep inspiration. Six days before admission the same pain recurred and persisted until her hospitalization. She also complained of rapidly progressive dyspnea on exertion, diaphoresis and fainting sensation. She denied fever, hemoptysis, the use of birth-control pills and smoking. Her serum cholesterol had been normal. The family history was noncontributory.

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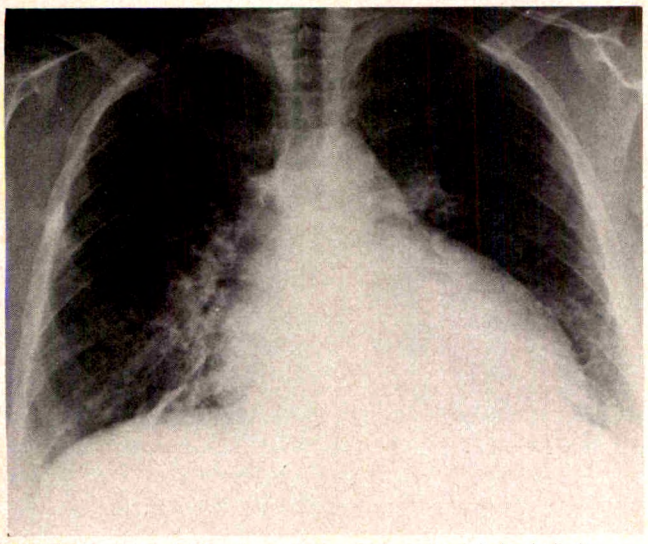

FIGURE 1. Case 1. Chest roentgenogram on hospital admission revealing a markedly enlarged cardiac silhouette.

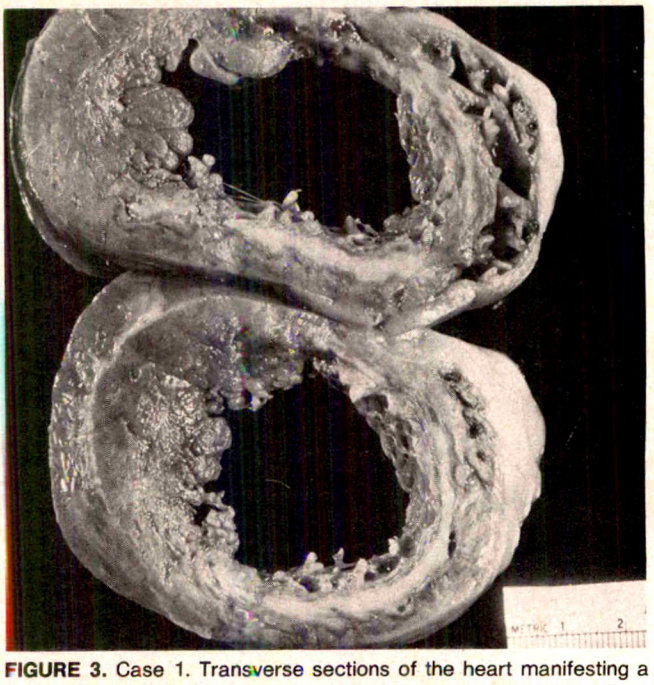

FIGURE 3. Case 1. Transverse sections of the heart manifesting a recent extensive myocardial infarct in the anterior and septal walls.

On physical examination she appeared acutely ill, tachypneic, diaphoretic and cold. The pulse was 140/min, regular and weak, the blood pressure was obtainable by palpation only at 60 mm Hg, the respiratory rate was 36/min and the temperature was 98°F. The skin was pale and clammy with livedo reticularis pattern. Jugular veins were not seen and no hepatojugular reflux could be demonstrated. The lungs were clear. Examination of the heart revealed normal heart sounds and a loud diastolic gallop; no pericardial rub or murmurs were heard. The abdomen was obese with striae.

Laboratory studies disclosed the following: hemoglobin 10.6 g/100 ml, hematocrit 31 percent, white blood cell count 5,400/mm^3, 2+ proteinuria, blood urea nitrogen 23 mg/100

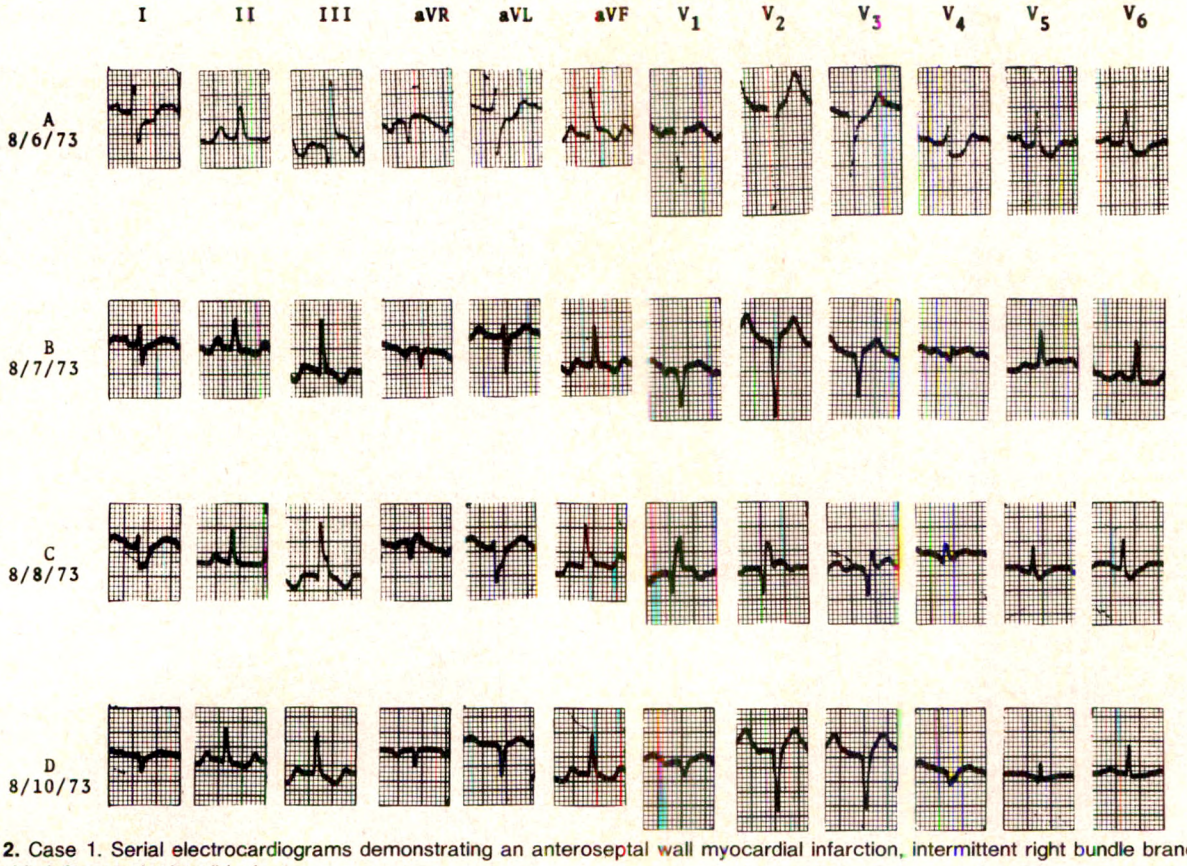

FIGURE 2. Case 1. Serial electrocardiograms demonstrating an anteroseptal wall myocardial infarction, intermittent right bundle branch block and probable left posterior hemiblock.

ml and serum creatinine 1.4 mg/100 ml. The serum electrolytes, uric acid, protein and cholesterol findings were normal. The initial serum enzyme values were: glutamic oxaloacetic transaminase (SGOT) 75 *U* (normal up to 45 *U*) and creatine phosphokinase (CPK) 410 *U* (normal up to 125 *U*). The chest roentgenogram revealed a markedly enlarged cardiac silhouette (Fig. 1). The electrocardiogram disclosed sinus tachycardia, right axis deviation, QS pattern in leads V_1 to V_3, S-T elevation in leads III and aVF and S-T depression in leads I, aVL and V_3 to V_6 (Fig. 2).

An emergency pericardiocentesis was performed, but no fluid was obtained. After administration of isoproterenol and hydrocortisone the blood pressure increased to 80/60 mm Hg. A repeat chest X-ray film revealed fluid in the left costophrenic angle, and small doses of furosemide were given.

Serial electrocardiograms disclosed changes consistent with an acute anteroseptal myocardial infarction; complete right bundle branch block appeared intermittently. The serum CPK increased to 2,100 *U*, SGOT to 360 *U* and lactic dehydrogenase (LDH) to 330 *U*. On the 2nd day the pain was mild during deep inspiration and when the patient was supine. She required isoproterenol to maintain blood pressure. On the 5th day ventricular fibrillation developed and all resuscitative efforts were unsuccessful.

Autopsy findings: The heart was enlarged, weighing 400 g. An extensive fibrinous pericarditis was present. A large recent transmural myocardial infarct involved the entire anterior wall and interventricular septum of the left ventricle from the cardiac apex to 1 cm below the base of the aortic valve (Fig. 3). A healed infarct, 3 cm in diameter, involved the posterior wall and posterior septum.

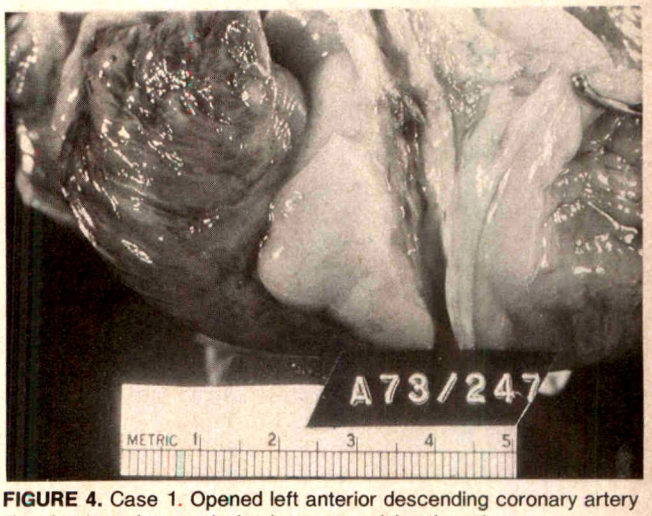

FIGURE 4. Case 1. Opened left anterior descending coronary artery showing complete occlusion by an organizing thrombus.

The coronary arteries displayed focal, but severe atherosclerosis. The left anterior descending coronary artery was completely occluded by an organizing thrombus 3 cm distal to its origin (Fig. 4). This thrombus was superimposed upon a hemorrhagic intimal atheroma (Fig. 5A). An atheromatous plaque with superimposed thrombus significantly narrowed the right coronary artery 4.5 cm from its ostium (Fig. 5B). Microscopic sections of coronary arteries revealed eccentric intimal fibrosis and dystrophic calcification (Fig. 5C). There was no inflammation or fibrinoid ne-

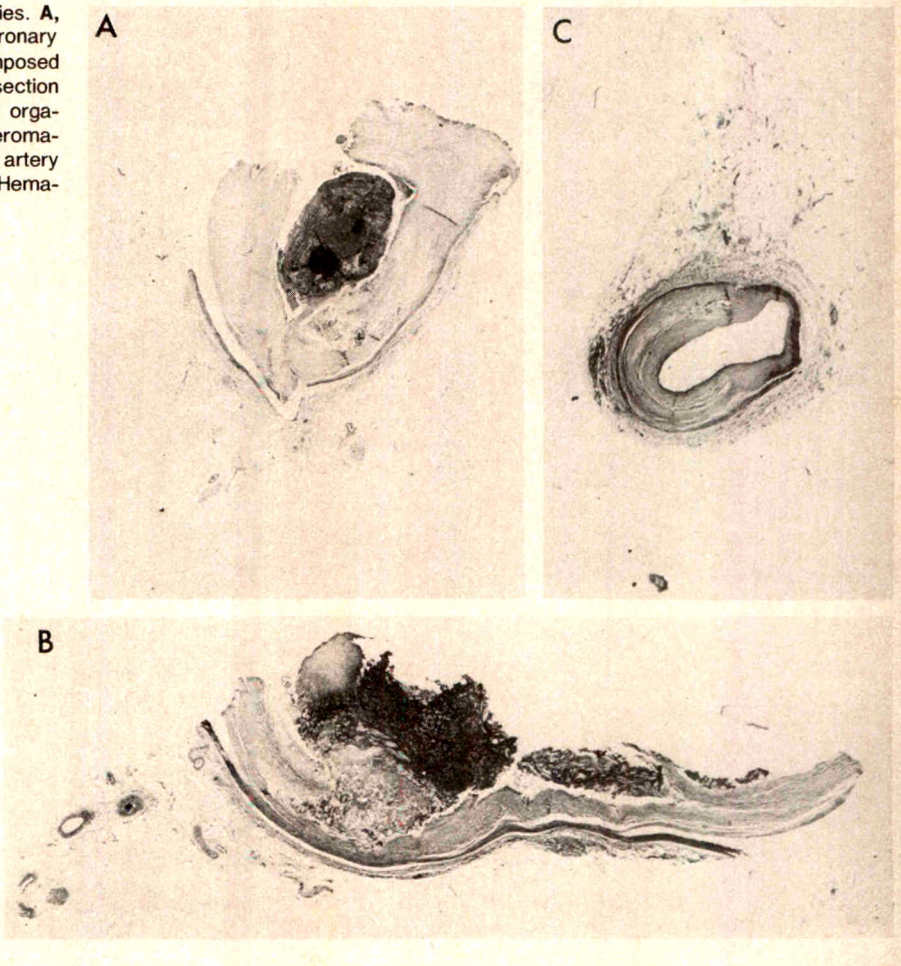

FIGURE 5. Case 1. Sections of coronary arteries. **A,** cross section of the left anterior descending coronary artery showing an occlusive thrombus superimposed upon an atheromatous plaque. **B,** longitudinal section of the right coronary artery showing an early organizing occlusive thrombus attached to an atheromatous plaque. **C,** cross section of a coronary artery manifesting severe eccentric intimal fibrosis. (Hematoxylin-eosin ×10.)

crosis in the coronary vessels. Immunofluorescent staining of a coronary artery revealed no gamma globulin or complement deposition.

Multiple 1 to 3 mm pink verrucae were attached to the atrial surface of both mitral valve cusps. Multiple similar verrucae covered the atrial and ventricular surfaces of all cusps of the tricuspid valve and, by extension, the adjacent right atrial and right ventricular endocardium. Microscopically these verrucae consisted of thrombi in various stages of early organization. Valvular destruction or microorganisms were not observed.

Several extracardiac anatomic findings characteristic of systemic lupus erythematosus were seen: mild focal glomerulonephritis with immune complex deposition within glomerular capillary walls, "onion-skin" periadventitial fibrosis of medium-sized splenic arteries and a focal interstitial pulmonary infiltration.

Case 2: A 24 year old man with systemic lupus erythematosus was admitted several times to Mount Sinai Hospital because of neurologic symptoms. His electrocardiogram revealed an anteroseptal wall myocardial infarction pattern in serial tracings, but he had no symptoms referable to the heart (Fig. 6).

Case 3: A 24 year old woman with systemic lupus erythematosus was admitted several times to Mount Sinai Hospital because of neurologic, dermatologic and renal symptoms. A pattern of inferior wall myocardial infarction developed in serial electrocardiograms, but she had no cardiac symptoms (Fig. 7).

Discussion

Cardiac symptoms are seen in 50 to 89 percent of patients with systemic lupus erythematosus,[3–10] but are rarely the first manifestation of the disease.[10,11] The most frequent cardiac diagnoses in these patients are pericarditis and myocarditis; both are found more frequently in autopsy than in clinical studies.[3,5,12] Electrocardiographic abnormalities are also common,[2,4,7,12] usually consisting of S-T segment and T wave changes secondary to pericarditis, myocarditis or metabolic abnormalities caused by the basic disease. Abnormal Q waves indicating myocardial infarction are very rare, even in patients found to have myocardial infarction at autopsy.[8]

Libman-Sacks valvulitis can be diagnosed with

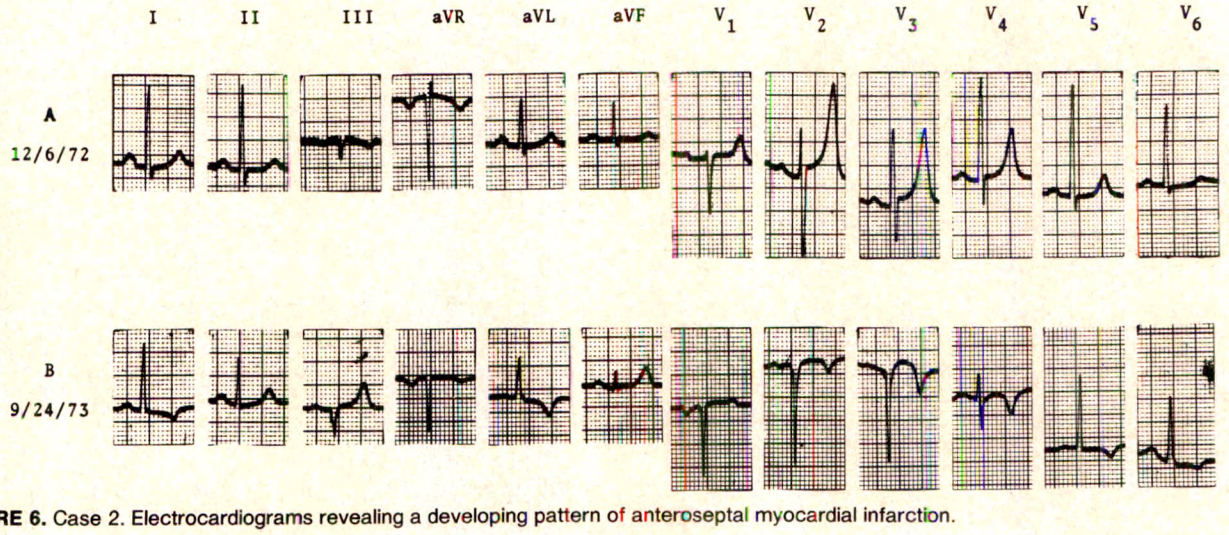

FIGURE 6. Case 2. Electrocardiograms revealing a developing pattern of anteroseptal myocardial infarction.

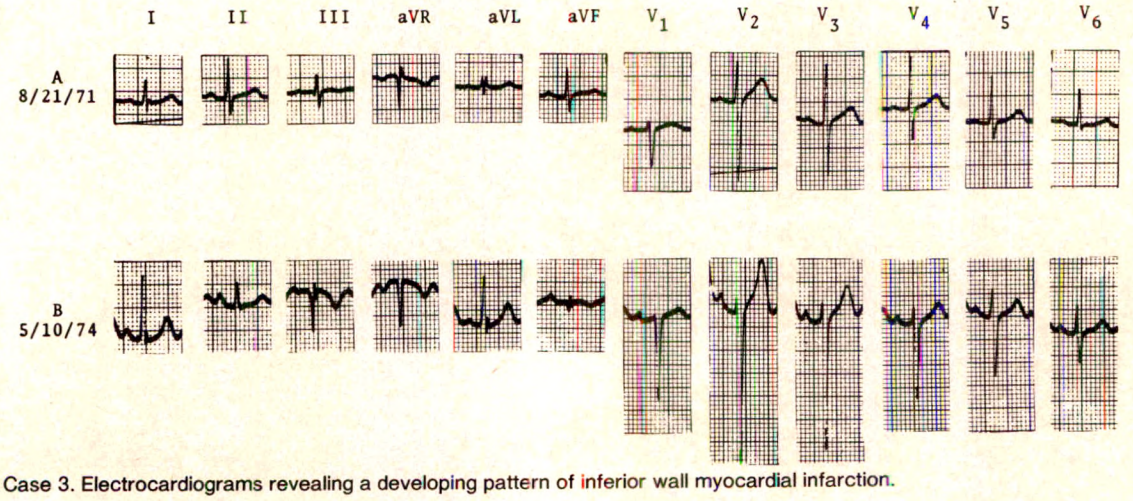

FIGURE 7. Case 3. Electrocardiograms revealing a developing pattern of inferior wall myocardial infarction.

certainty only at autopsy,[9] and its reported incidence has been reduced in the last 2 decades.[13,14] Some[2,9,11] have attributed this decreased incidence to corticosteroid treatment, but others[10] believe that steroid therapy has not been a factor.

In several large clinical series, totaling 1,186 patients with systemic lupus erythematosus, with 147 autopsies,[2,4–7,9,12] myocardial infarction was not reported. Among their patients with lupus erythematosus Taubenhaus et al.[15] found two with angina pectoris, one a 53 year old woman with electrocardiographic criteria for myocardial infarction. Since autopsy was not performed the coronary artery disease in these patients cannot be characterized.

Coronary atherosclerosis and myocardial infarction in lupus: Coronary arteritis was the cause of myocardial infarction in a 35 year old woman with systemic lupus erythematosus described by Dubois[16] and in a 16 year old youth observed by Bonfiglio et al.[17] The latter suspected coronary arteritis in three other patients found to have coronary artery disease on arteriographic studies performed because of angina pectoris; later one had a myocardial infarction. Brigden et al.[8] found myocardial infarction in 2 of 27 autopsies of patients with lupus erythematosus, in both cases associated with widespread arterial occlusions and acute necrotizing lesions in the small vessels. Hejtmancik et al.[10] described coronary arteritis in 6 of 16 autopsies of patients with systemic lupus erythematosus, but no patient had myocardial infarction due to such involvement. Six of their 142 patients had angina pectoris; 4 of the 6 had an electrocardiographic pattern of myocardial infarction without a history of it, but one died and was found to have coronary atherosclerosis and myocardial infarction at autopsy.

Kong et al.[11] described two patients, 42 and 46 years old, respectively, with myocardial infarction due to coronary atherosclerosis in 30 autopsies of patients with systemic lupus erythematosus. Tsakraklides et al.[18] cited a 29 year old woman with lupus erythematosus who died of acute myocardial infarction and who had marked atherosclerosis in the major coronary trunks without signs of active or healed arteritis. This case and our Case 1, both describing young women without underlying risk for coronary atherosclerosis, suggest an association between systemic lupus erythematosus and coronary atherosclerosis that is probably not coincidental, considering the very low incidence of myocardial infarction in persons under age 30. In this age group the incidence of myocardial infarction in women is much lower than in men[19–21]; of 398 patients of three series with myocardial infarction at age 40 or less only 1 woman was less than 30 years old and she had severe diabetes of juvenile onset and hyperlipidemia.[20]

Pathogenesis of coronary atherosclerosis in lupus: The mechanism by which systemic lupus erythematosus may influence the development of coronary atherosclerosis is not known. Rich and Gregory[22] described sclerotic lesions of the coronary arteries in lupus erythematosus, indistinguishable from ordinary atherosclerosis in its more advanced and fibrous form. They proposed an antigen-antibody reaction as the pathogenesis of these lesions.

The influence of corticosteroids in coronary atherosclerosis is not clear. Necrotizing arteritis has been reported in patients with rheumatoid arthritis treated with steroids.[23,24] Kemper et al.[25] found lesions of periarteritis nodosa in 4 of 14 patients with rheumatoid arthritis treated with steroids, whereas none of the 38 patients who did not receive steroids had such lesions; there was no correlation between dosage or duration of treatment and the appearance of vascular lesions. However, they did not mention atherosclerotic lesions in their cases. The latter were not found at autopsy in Finck's patient[26] with rheumatoid arthritis and necrotizing arteritis supposedly due to overdosage of cortisone.

Autopsy in our Case 1 revealed atherosclerosis, but the other two patients with electrocardiographic pattern of myocardial infarction could have either coronary atherosclerosis or arteritis, and there is no way to differentiate, clinically, between them. This distinction may become important if coronary arterial surgery is ever contemplated in these young patients. Further clinical, arteriographic and pathologic correlations will be necessary to clarify this problem.

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Bilateral Arteriosclerotic Coronary Arterial Aneurysms Successfully Treated with Saphenous Vein Bypass Grafting

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A man with ischemic heart disease was discovered to have bilateral coronary arterial aneurysms that were successfully treated with saphenous vein grafting. Preoperative coronary arteriograms revealed a tight luminal stenosis at the proximal end of the large aneurysm in the left anterior descending artery, suggesting poststenotic dilatation as an etiologic or contributing factor. The right coronary artery was totally occluded proximally, but was noted to be aneurysmal at operation. This is the 14th published case of nonfistulous coronary arterial aneurysm diagnosed in vivo, and the first associated with proximal luminal stenosis.

In 1761 Morgagni[1] provided the first pathologic description of aneurysmal dilatation of the coronary arteries. The first report of a case diagnosed antemortem[2] did not appear until almost 200 years later, but several such cases have been described since the advent of coronary arteriography. We recently encountered a patient with bilateral coronary arterial aneurysms of apparent arteriosclerotic origin. The diagnosis was made preoperatively and the patient was successfully treated with aortocoronary saphenous vein graft surgery.

Case Report

A 48 year old white male laborer had a subendocardial infarction in July 1971. He was initially seen by us in September 1972 when he was hospitalized with an acute inferior transmural myocardial infarction. Several days after admission a systolic sound was heard at the left sternal border by one examiner. This sound was thought to represent a murmur but may have been a pericardial rub; it was not noted on previous or subsequent examinations. During the 2nd week of convalescence the patient began to experience angina pectoris on minimal activity. About the same time, melena was noted; the patient's hemoglobin was 5.6 g/100 ml. Although gastrointestinal X-ray examination revealed no abnormality, the bleeding was presumed to be secondary to a nonvisualized gastric stress ulcer complicated by anticoagulation with sodium warfarin. Administration of warfarin was discontinued, and there was no further evidence of gastrointestinal bleeding. The angina pectoris was relieved when the hemoglobin was normalized by a transfusion of packed red blood cells.

Two months later the patient was readmitted because of coronary insufficiency syndrome. Physical examination was noncontributory except for an audible atrial gallop. Serial electrocardiograms and serum enzyme determinations revealed no new myocardial damage. The chest X-ray film disclosed only mild left ventricular prominence. Hemoglobin was 15.8 g/100 ml.

Cardiac catheterization was performed utilizing the transfemoral percutaneous route. The resting supine left ventricular pressure was 129/16–30 mm Hg. The left ventriculogram revealed increased end-systolic and end-diastolic volumes. There was akinesis of the inferobasal segment of the left ventricular wall, and the anterior wall was diffusely hypokinetic. Selective left coronary arteriograms revealed a widely patent proximal left main coronary artery. The left circumflex coronary artery had at its origin a 90 percent stenosis with mild poststenotic dilatation; the remainder of the vessel was normal.

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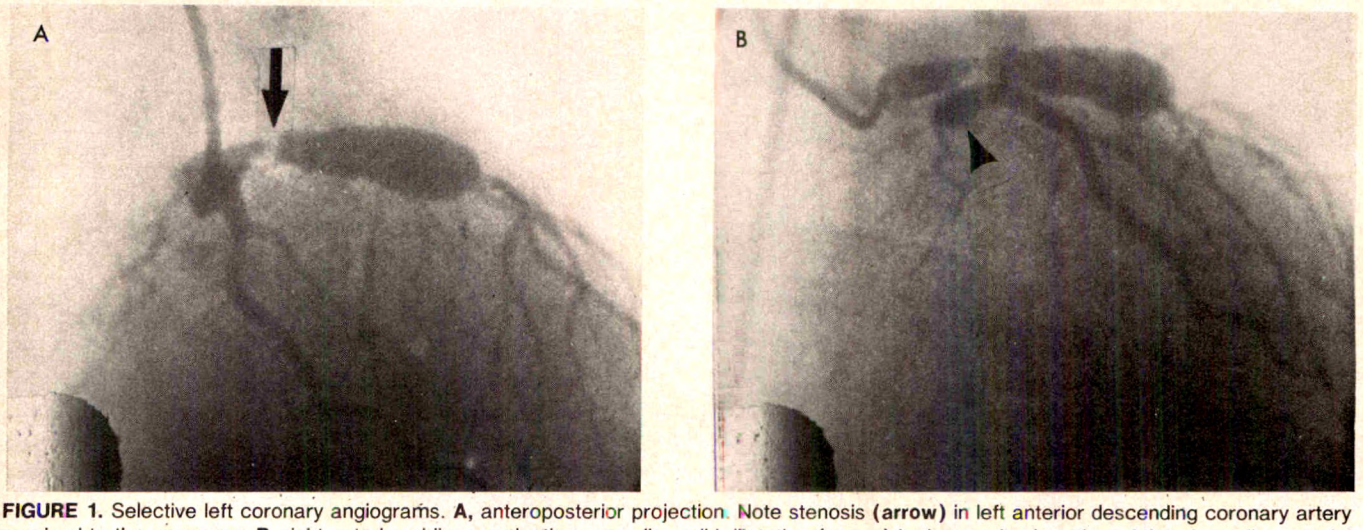

FIGURE 1. Selective left coronary angiograms. **A,** anteroposterior projection. Note stenosis **(arrow)** in left anterior descending coronary artery proximal to the aneurysm. **B,** right anterior oblique projection, revealing mild dilatation **(arrow)** in the proximal portion of the circumflex arterial system.

In the proximal portion of the left anterior descending artery there was a localized stenosis of more than 90 percent (Fig. 1). Distal to this stenosis there was a large aneurysm (up to 1.5 cm in internal diameter) that appeared to involve the entire proximal third of the left anterior descending artery. At least two septal perforator branches were seen arising from the inferior wall of the aneurysm, and two small diagonal branches arose from the posterior wall. At the junction of the aneurysm with the distal segment of the left anterior descending artery, there was another stenosis of more than 90 percent. The distal segment of this artery had an estimated internal diameter of only 1 mm. The right coronary artery was completely occluded 1 cm from its origin. There was no antegrade filling of the distal right coronary artery on injection into the right coronary orifice. The posterior descending branch of the right coronary artery was seen filling retrograde during injection into the left coronary artery.

Aortocoronary saphenous vein bypass graft surgery was performed with insertion of vein grafts into the left circumflex and distal left anterior descending coronary arteries. The area of aneurysmal dilatation in the proximal left anterior descending coronary artery was clearly visualized at operation, and estimated to be 2.5 cm wide and 4 cm long. There was an extensive irregular aneurysm of the proximal and middle thirds of the right coronary artery (Fig. 2). The aneurysmal segment of the right coronary artery was estimated to be 2 cm wide and 6 cm long. No vein graft was inserted into the right coronary artery because the distal segment was considered technically unsuitable for grafting. The postoperative course was uneventful; serum enzyme determinations and electrocardiographic criteria revealed no evidence of postoperative myocardial infarction.

The patient had no further cardiac symptoms until April 1973, when he had mild congestive heart failure that responded satisfactorily to therapy with digitalis and diuretic agents. In May 1973, he had his first and only recurrence of substernal chest pain while he was casting for fish; the pain was severe, and was associated with nausea, vomiting and dyspnea. He was hospitalized but there were no electrocardiographic changes and serum enzyme determinations were within normal limits. The episode was considered a manifestation of coronary insufficiency syndrome. Repeat arteriographic studies were not performed.

Discussion

Prevalence: Although coronary arterial aneurysms without arteriovenous fistula are seldom recognized before death, they are not an extremely rare entity, as shown by autopsy studies. Daoud et al.[3] found 10 hearts with aneurysms of the coronary arteries in 694 consecutive autopsies on persons 16 years of age or older at the time of death (frequency of 1.4 percent). These authors compiled a total of 89 cases, including their own series, of coronary arterial aneurysm diagnosed post mortem. Forty-eight of the 89 cases (52 percent) were considered arteriosclerotic, and 16 (18 percent) congenital in origin. In 83 of the 89 cases the immediate cause of death was presumably related to the cardiovascular system, but in only 16 cases was it thought to be directly related to the presence of the aneurysm.

In 1958, Munker et al.[2] reported the first case of coronary arterial aneurysm to be documented in vivo by angiography. Their case had an arteriovenous fistula associated with the aneurysm. In 1964, Barclay et al.[4] described a 54 year old man with multiple nonfistulous coronary arterial aneurysms. The diagnosis was made post mortem, but the authors observed retrospectively that an antemortem diagnosis might have been possible on the basis of multiple calcific rings noted along the right heart border in the conventional chest roentgenogram. The first two reports of nonfistulous coronary arterial aneurysm diagnosed antemortem appeared in 1967[5,6]; an additional 11 cases have since been reported.[7–17] To the best of our knowledge, our patient represents the 14th reported case of nonfistulous coronary arterial aneurysm diagnosed antemortem and documented in vivo by angiography.

Only 2 of the 14 cases diagnosed antemortem (14 percent) were thought to have an arteriosclerotic origin,[7,18] compared with 52 percent of the 89 cases with a post mortem diagnosis compiled by Daoud et al.[3] Eight of the 14 cases diagnosed antemortem were

thought to be congenital,[5,6,8,9,14–17] compared with only 18 percent of the postmortem series. These findings suggest that arteriosclerotic aneurysms of the coronary arteries are more often incidental autopsy findings, whereas congenital aneurysms are more likely to produce symptoms directing clinical attention to the heart.

Clinical features: Chest pain compatible with myocardial ischemia or infarction, or both, was reported in 10 of the 14 cases diagnosed antemortem.[5–9,12,15–18] Of the other four, one young man with bilateral mycotic coronary arterial aneurysms had chest pain that may have been related to pericarditis,[10] one infant had congestive heart failure without apparent pain[13] and the other two patients had no symptoms referable to the heart.[11,14] In eight cases systolic precordial murmurs were noted on at least one occasion,[5,7,8,10,13,15,17,18] but in five of these cases the murmur may not have been directly related to the aneurysm.[7,10,13,15,18] In four cases diastolic murmurs were described.[5,8,14,17] One patient had an abnormal systolic impulse at the left sternal border, apparently due to pulsation of the large left coronary arterial aneurysm.[14]

The electrocardiogram taken before angiography was normal in only one case, and that patient had no cardiac symptoms.[14] Six patients had electrocardiographic evidence of previous infarction, and each had aneurysmal involvement of the vessels corresponding to the area of infarction.[6,9–11,15,18] In 5 of the 14 patients, the conventional chest roentgenogram provided information pertinent to the presence of coronary arterial aneurysm.[10–12,14,15] Two patients[10,14] had a mass on the left heart border, and one[12] had fullness in the region of the pulmonary outflow tract; an aneurysm was found in the corresponding location in each. The patient of Ghahramani et al.[15] had an intracardiac ring of calcification on chest X-ray examination, reminiscent of the cases diagnosed post mortem by Barclay et al.[4] and Andersen and Wennevold.[19] The chest X-ray film of the patient of Konecke et al.[11] revealed a shotgun pellet at the site of a traumatic coronary arterial aneurysm.

Location of aneurysms: Seven of the 14 patients had a single coronary arterial aneurysm[5,8,9,11,12,14,15]; the other 7 had multiple aneurysms,[6,7,10,13,16–18] and in 6 of these patients the aneurysms were bilateral.[6,7,10,13,16,18] The involved arteries included all of the main coronary vessels (left main, left anterior descending, left circumflex and right coronary arteries); in two instances[7,17] secondary branches were also involved (diagonal branch of the left anterior descending and atrial branch of the right coronary artery). Our case is the only one in which stenosis of the coronary artery was noted at the proximal end of the aneurysm, suggesting poststenotic dilatation as an etiologic or contributing factor.

Surgical treatment: Eight of the 14 patients underwent coronary arterial surgery[5,8,10,12,14–16,18]; in two cases, each with a single large saccular aneurysm arising laterally from the wall of the distal left anterior descending artery, the aneurysms were surgically excluded with apparently satisfactory results.[5,8]

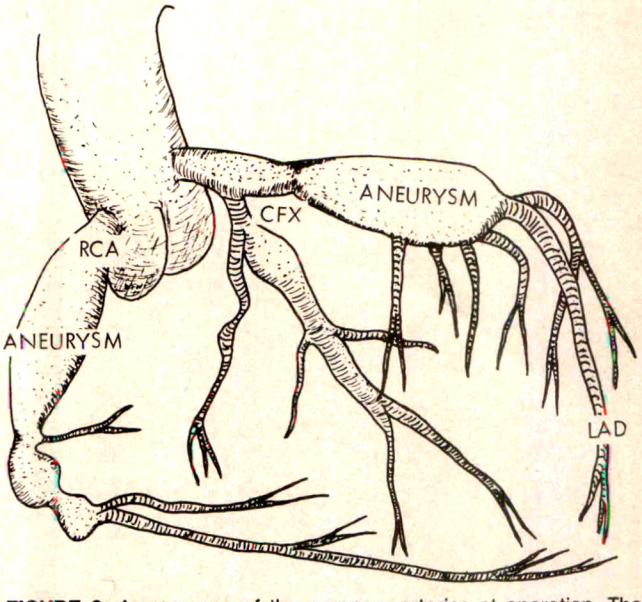

FIGURE 2. Appearance of the coronary arteries at operation. The drawing depicts external appearance; hence, luminal stenoses are not illustrated. CFX = circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

In the case of Cliff et al.,[10] bilateral false coronary arterial aneurysms of mycotic origin were successfully removed by excision. In two other cases,[12,14] a single large aneurysm was excised and an interposed vein graft was inserted to reestablish continuity of the artery. Follow-up coronary angiograms demonstrated patent grafts in both cases, but one[14] had an acute intraoperative infarct possibly related to sacrifice of branch vessels arising from the aneurysm.

Three patients, including our own, underwent aortocoronary saphenous vein bypass grafting with insertion of grafts distal to the aneurysms.[15,16,18] Two of the three patients[15,16] had postoperative angiograms that demonstrated patency of the graft and the distal arterial segment. In the case of Mattern et al.[16] the angiogram obtained 18 months postoperatively demonstrated both new aneurysmal dilatation of the posterior descending branch distal to the patent graft to the right coronary artery and extension of the aneurysm in the nongrafted left coronary artery. This disconcerting observation suggests a diffuse structural defect of the coronary arterial walls. It remains to be seen whether a similar problem will arise in other patients operated on for coronary arterial aneurysm.

Postoperative thromboembolism: In the cases reported by Ebert et al.[12] and Dawson and Ellison,[14] friable clot was found in the aneurysms at operation. Before operating on our patient, we considered ligation of the left anterior descending coronary arterial aneurysm at its distal end to prevent embolization from the aneurysm into the distal grafted segment. We also considered the possibility that ligation of the aneurysm distally might reduce blood flow sufficient-

ly to result in thrombosis of the aneurysm and occlusion of the septal and diagonal branches arising from it. We elected not to ligate the aneurysm. We did initiate long-term anticoagulant therapy with sodium warfarin. Eight months postoperatively the patient had an episode of chest pain compatible with myocardial ischemia but without evidence of new myocardial damage. This event may have been the result of embolization from the aneurysm. Since recurrent embolization into the distal portion of the left anterior descending coronary artery could have a fatal outcome, we have concluded in retrospect that it probably would have been preferable to ligate the distal end of the aneurysm. Embolization can also be prevented by excising the aneurysm and inserting an interposed vein graft, but this surgical approach should probably be limited to instances in which there are no significant branches arising from the aneurysm.

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Bilateral Nonfistulous Congenital Coronary Arterial Aneurysms

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A 15 year old boy collapsed and died after participating in a basketball game. Autopsy revealed bilateral congenital coronary arterial aneurysms. The diagnosis was made post mortem but, retrospectively, might have been suspected during life, even before angiography. The clues to the correct diagnosis were chest pain, a systolic and diastolic murmur and a mass on the right heart border in the chest roentgenogram.

Nonfistulous congenital aneurysm of a coronary artery is a relatively rare disorder. In those few cases in which the diagnosis has been made antemortem, it has usually been an unexpected finding on coronary arteriography. We recently encountered an unusual case of bilateral congenital coronary arterial aneurysms that was initially diagnosed post mortem but which in retrospect could have been suspected antemortem on the basis of clinical information and routine chest X-ray examination.

Case Report

A 15 year old white boy suddenly collapsed and died after participating in a basketball game. At autopsy an unusual abnormality of the coronary arteries was noted. Since the death and autopsy had occurred in a small farming community, the heart was removed and sent to us for evaluation. The following information was obtained by us from the boy's family and from the records of physicians who had previously examined him.

The boy was the second of two children of a farming family. There is no family history of cardiac disease. His mother definitely recalled having a severe influenza-like illness in the first trimester of pregnancy, but the pregnancy was otherwise normal and was carried to term; the delivery was uneventful. The boy was born with a cleft lip but no cardiac abnormality was noted at birth; his growth and development were normal.

The cleft lip was surgically repaired at age 2 months, and the repair was surgically revised at age 6 years, under the auspices of the Nebraska Crippled Children Program. As part of the follow-up evaluation under this program, he was examined by either one of two pediatricians at approximately yearly intervals from 1962 to November 1971. Neither examiner noted any cardiac abnormality. Routine posteroanterior chest roentgenograms were taken as part of these evaluations in 1963, 1967 and 1970; the first two were normal, but the third, taken in 1970, revealed an abnormal convexity in the right heart border (Fig. 1). This abnormality was noted in the radiologist's report, but it was not investigated further.

In June 1972, 3 months before his death, the patient complained for the first time of chest discomfort that occurred intermittently, apparently unrelated to effort, for about 2 weeks. During the next 3 months he had chronic fatigue but continued to help his father with farm work and was able to perform heavy labor without apparent difficulty. On a routine preschool physical examination in September 1972, definite cardiac abnormalities including a prominent precordial impulse were noted. The precordial cardiac impulse was not hyperactive. A grade 5/6 harsh murmur filling systole and diastole was audible over the entire precordium but did not radiate into the carotid arteries. The murmur was greatly accentuated during exercise. Blood pressure was normal in both arms. No chest X-ray film or electrocardiogram was ob-

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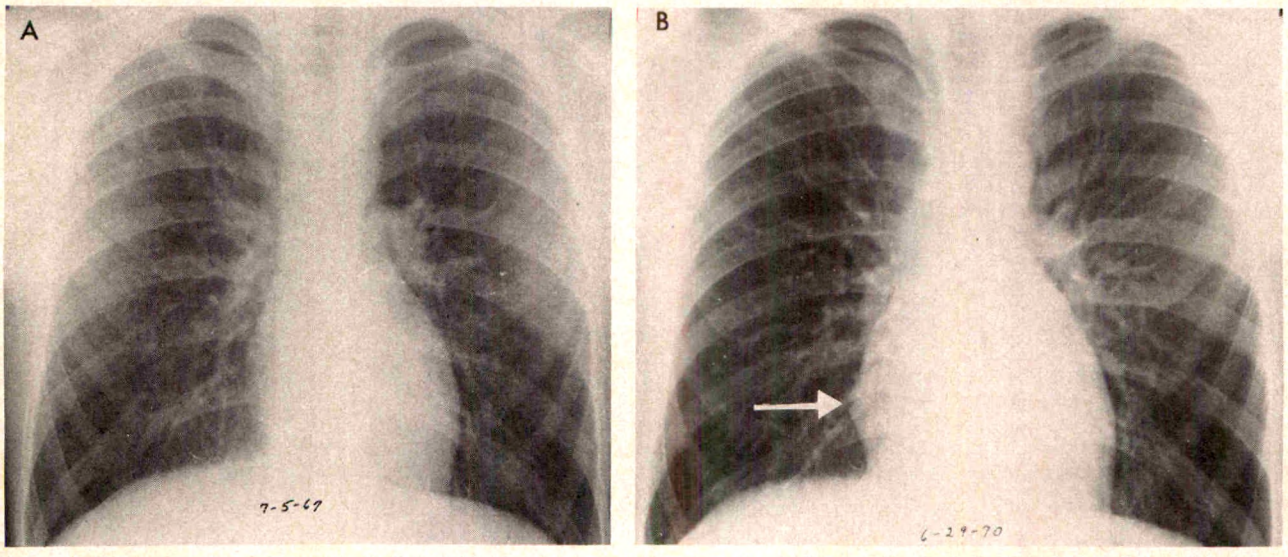


FIGURE 1. Chest roentgenograms. **A,** July 5, 1967, interpreted as normal. **B,** June 29, 1970, revealing a change from the previous film. There is a localized protrusion along the right heart border **(arrow)** representing the largest of the aneurysmal dilatations of the right coronary artery found at autopsy.

tained. The patient was referred to his family physician, but no further investigation was carried out, and he was not advised to restrict his activity. On November 3, 1972, he participated in a basketball game at school without apparent difficulty; while getting dressed afterward, he suddenly collapsed and died.

Pathologic Findings

Description of the heart: The heart weighed 384 g. The ventricular cavities were not dilated. The left ventricular wall thickness was 1.4 cm and the right ventricular wall thickness was 0.5 cm. A grossly visible area of subendocardial fibrosis in the posterior left ventricular wall measured 1.3 by 2.8 cm. A second and separate area of confluent focal subendocardial fibrosis on the posteroinferior aspect of the septum measured 1.0 cm in diameter. Other small areas of patchy subendocardial fibrosis involved the left ventricular wall, but there was no transmural myocardial scarring. There was no grossly visible scarring of the papillary muscles.

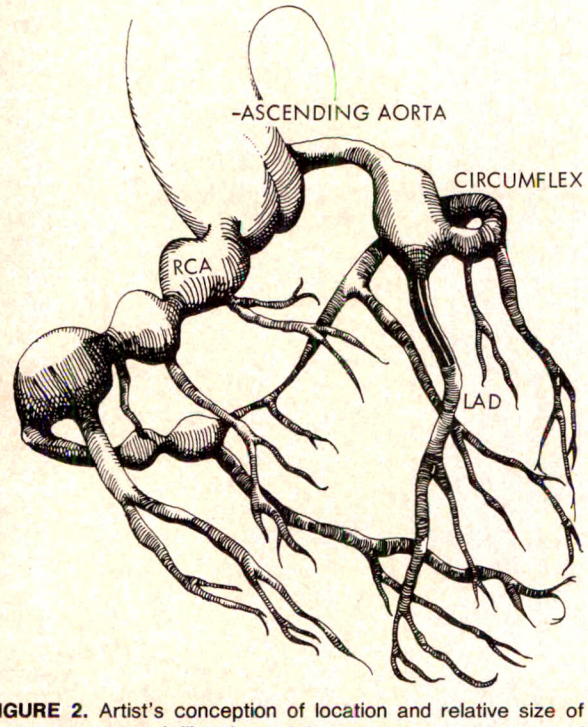


FIGURE 2. Artist's conception of location and relative size of the various aneurysmal dilatations of the coronary arterial system. Note occlusion (with recanalization) of the left anterior descending artery distal to the aneurysm. LAD = left anterior descending coronary artery; RCA = right coronary artery.

Coronary arteries: The multiple aneurysms of the right coronary artery were conspicuous on gross inspection of the heart before dissection. Dissection of the right coronary artery revealed a normal-sized ostium. Starting immediately distal to the ostium there were three consecutive saccular aneurysms, the third occurring at the level of the acute marginal branch (Fig. 2 and 3A). Between the first and second aneurysms, and again between the second and third aneurysms, the vessel lumen narrowed to 3 to 4 mm in internal diameter, approximately normal size. The first two aneurysms were 1.5 cm and the third was 2.5 cm in internal diameter. The walls of the aneurysms were thin, measuring only 1 mm in thickness. The first two aneurysms were free of clot, but the third and largest aneurysm was filled with laminated thrombus. No lumen could be identified between the third aneurysm and the segment of artery distal to the aneurysm. When the heart was viewed in the normal anatomic position, the third and largest aneurysm was seen on the right border of the heart and probably produced the convexity in this area observed in the most recent chest roentgenogram (Fig. 1B). Distal to the third aneurysm, the main right coronary artery continued in the atrioventricular groove for about 3 cm; at this point there was a fourth aneurysm with an internal diameter of 0.6 cm, immediately followed by a fifth aneurysm with an internal diameter of 1.1 cm. Both of these aneurysms were free of clot. The fifth aneurysm involved the origin of the posterior descending branch as well as the continuation of the right coronary artery in the atrioventricular groove.

The ostium and the initial 1.5 cm of the left main coronary artery were normal. The distal left main coronary artery and its bifurcation were aneurysmal (Fig. 2 and 3B). The aneurysm measured 1.2 cm in internal diameter and

extended into the proximal left anterior descending and left circumflex coronary arteries. The aneurysm itself was free of clot. The proximal 2 cm of the left anterior descending artery was involved with fibrous occlusive process and had a narrow recanalized lumen less than 1 mm in diameter. The distal left anterior descending artery was normal. The left circumflex artery was normal distal to the aneurysm at its origin. The left circumflex artery was nondominant, but had three medium-sized branches to the lateral and posterior left ventricular wall.

Microscopic findings: Histologic sections were obtained from the aorta and from aneurysmal and nonaneurysmal portions of the coronary arteries; staining was performed with elastic, hematoxylin-eosin, van Gieson and periodic acid-Schiff (PAS) stains. The nonaneurysmal portions of the coronary arteries manifested an intact media, but there was marked intimal thickening, characterized by the presence of fibroblasts and elastic fibers (Fig. 4A). The proximal 2 cm of the left anterior descending artery showed obliterative fibrosis of the lumen with recanalization. The aneurysmal portions of the coronary arteries also showed marked intimal thickening but, in addition, several aneurysms manifested focal interruption of the media (Fig. 4B). The wall of the aneurysm involving the left coronary artery was formed by dense fibrous tissue with no medial elements identified (Fig. 4C). No inflammatory or atheromatous changes were noted in any of the vessels, and there was no PAS-positive material. When examined microscopically, sections from the left ventricular wall were normal except for areas of fibrosis with minimal cellular infiltration.

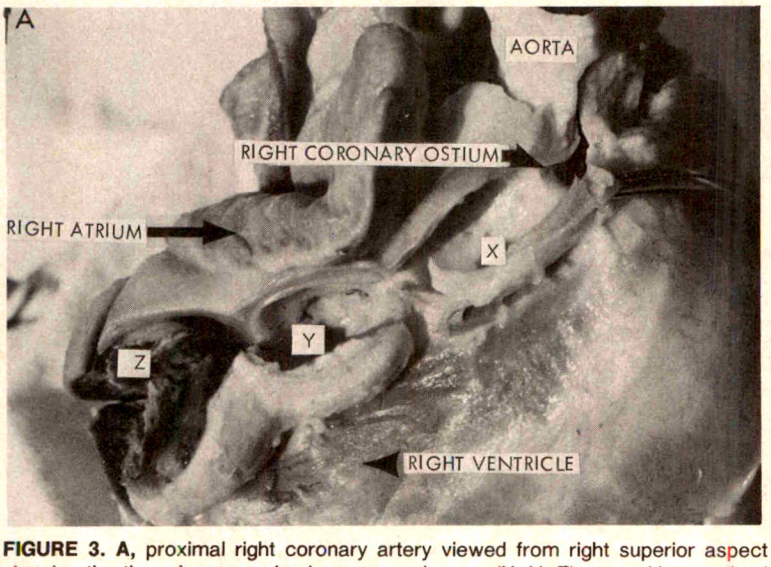
Discussion

Nonfistulous congenital coronary arterial aneurysm is a relatively rare disorder. Daoud et al.[1] compiled a total of 89 cases of coronary arterial aneurysm reported up to 1963, all of which were diagnosed post mortem. Only 16 of these were thought to be of congenital origin. The first two cases of nonfistulous congenital coronary arterial aneurysm diagnosed antemortem were reported in 1967 by Bjork and Bjork[2] and by Sherkat et al.[3] Wilson et al.[4] recently compiled 14 reported cases of nonfistulous coronary arterial aneurysm diagnosed during life. Eight[2,3,5–10] of these were considered by the original authors to be congenital.

Clinical Features

Most of the reported cases of coronary arterial aneurysm were diagnosed at autopsy or when the aneurysm was unexpectedly revealed by coronary arteriography. However, a review of the reported cases of congenital coronary arterial aneurysm diagnosed antemortem indicates some clinical features that should suggest this diagnosis. Most of the patients were children or young adults with chest pain, and half of them had diastolic or combined systolic and diastolic heart murmurs. Of the eight patients with nonfistulous congenital coronary arterial aneurysm diagnosed antemortem, six[3,6–10] were under 33 years of age at the time of diagnosis. All but one[7] of these eight patients presented with chest pain compatible with myocardial ischemia or infarction, or both. Four[2,5,7,10] of the eight patients had either a diastolic heart murmur or combined systolic and diastolic murmurs. Of the other four patients, three[3,6,9] had no murmur, and one[8] had an apical systolic murmur that may have represented mild mitral regurgitation.

The routine chest roentgenogram provided a clue to the diagnosis in several reported cases of coronary arterial aneurysm. In 1964, Barclay et al.[11] described



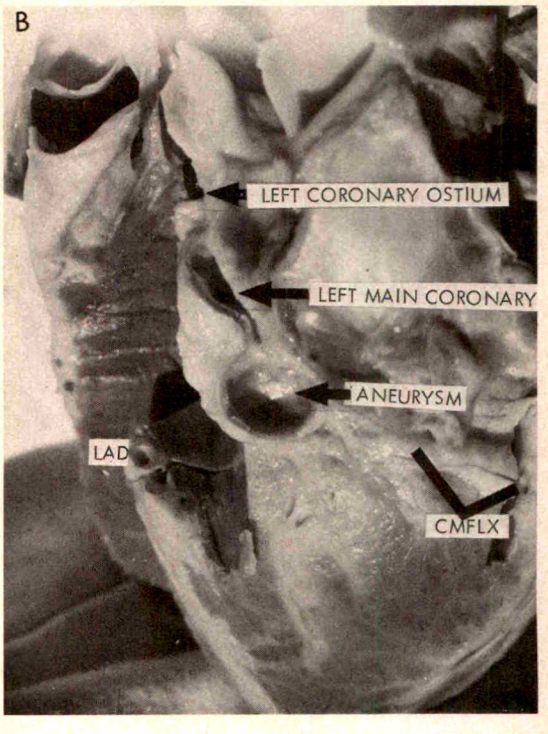


FIGURE 3. A, proximal right coronary artery viewed from right superior aspect showing the three large proximal aneurysmal areas (X, Y, Z), one with organized and recent thrombus (Z). The forceps is retracting the wall of the proximal aneurysm revealing the normal-sized right coronary ostium. **B,** proximal left coronary system viewed from the left superior aspect showing the left main coronary artery in its proximal aneurysmal segment. Sections of the left ventricular myocardium have been removed for study and the distal left anterior descending artery is visible. The left coronary ostium is not well seen because the aortic wall was opened into the ostial area. CMFLX = circumflex coronary artery; LAD = left anterior descending coronary artery.

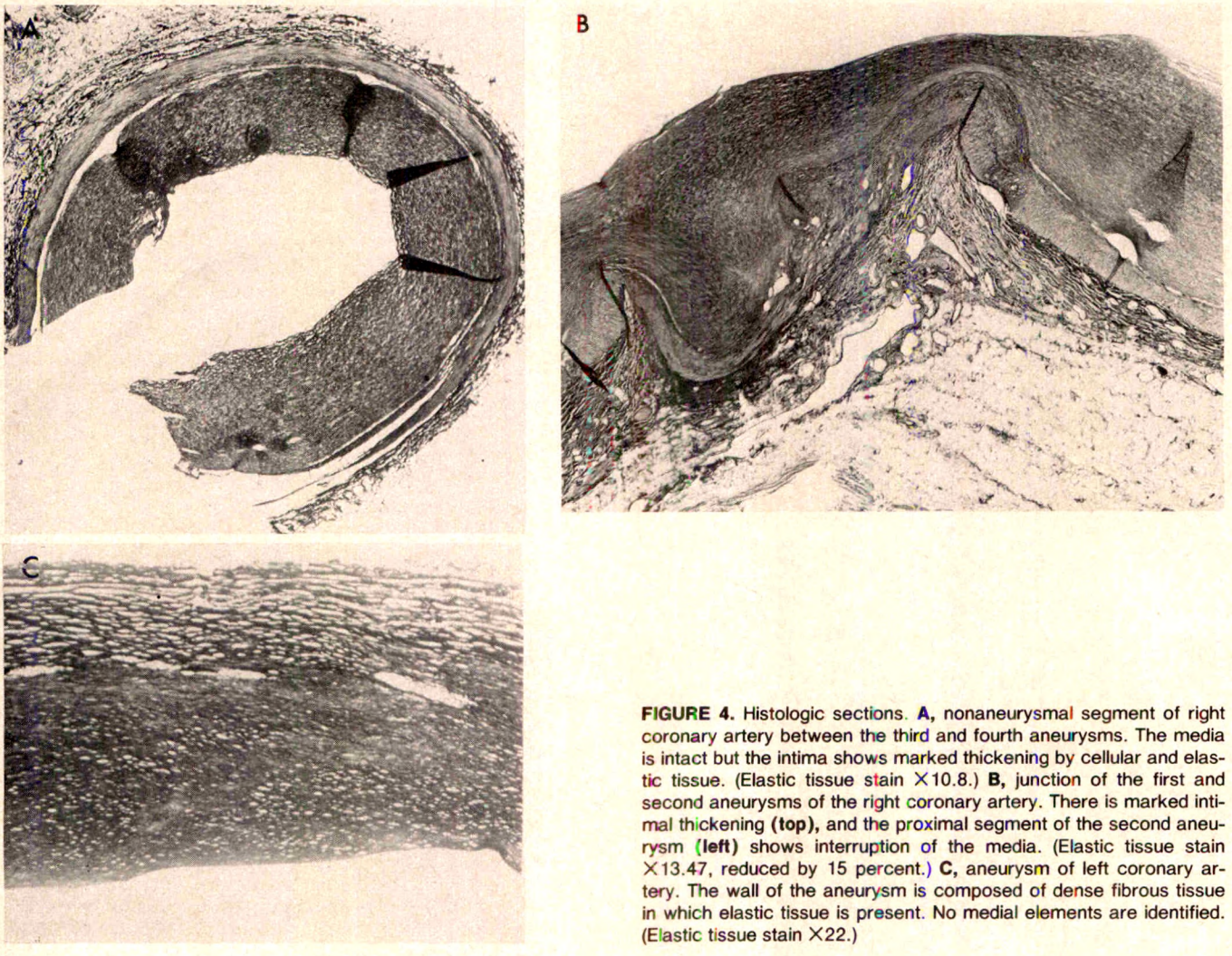


FIGURE 4. Histologic sections. **A,** nonaneurysmal segment of right coronary artery between the third and fourth aneurysms. The media is intact but the intima shows marked thickening by cellular and elastic tissue. (Elastic tissue stain ×10.8.) **B,** junction of the first and second aneurysms of the right coronary artery. There is marked intimal thickening **(top),** and the proximal segment of the second aneurysm **(left)** shows interruption of the media. (Elastic tissue stain ×13.47, reduced by 15 percent.) **C,** aneurysm of left coronary artery. The wall of the aneurysm is composed of dense fibrous tissue in which elastic tissue is present. No medial elements are identified. (Elastic tissue stain ×22.)

multiple nonfistulous coronary arterial aneurysms discovered at autopsy in a 54 year old man with chest pain. Although the correct diagnosis was not considered before death, the authors observed retrospectively that coronary arterial aneurysm could have been suspected on the basis of multiple calcific rings noted along the right heart border in the conventional chest roentgenogram. Andersen and Wennevold[12] reported a similar case in 1967, also diagnosed post mortem, with calcification in a coronary arterial aneurysm on the left heart border that was evident in the chest roentgenogram. Three of the 14 cases of coronary arterial aneurysm diagnosed antemortem reviewed by Wilson et al.[4] had abnormal convexity on the heart border in routine chest roentgenograms, at locations corresponding to aneurysms subsequently demonstrated by angiography. A fourth case had an intracardiac ring of calcification at the site of a coronary arterial aneurysm.

In our patient a definite, discrete convexity on the right heart border was observed in a chest roentgenogram taken in 1970, 2 years before death. This convexity was not present in the roentgenogram taken in 1967, thus suggesting that the aneurysm at that location was expanding during the 3 year interval. A mass on the heart border is certainly not specific for a diagnosis of coronary arterial aneurysm, and other disorders such as cyst or neoplasm would have to be considered. However, the appearance of a murmur in systole and diastole in a young patient with chest pain was an additional clue that should have suggested the correct diagnosis and led to cardiac catheterization and coronary arteriography.

Surgical Treatment

If the diagnosis had been made before death in this case, surgery would have been considered. A surgical approach has been used with some success in several reported cases of coronary arterial aneurysm.[2,4,5,7–9,13,14] In our case the right coronary artery may not have been suitable for aortocoronary saphenous vein grafting because of the diffuse involvement with multiple aneurysms, although it might have been possible to graft into the posterior descending branch. The left circumflex artery was technically suitable for saphenous vein grafting distal to the aneurysm at the

bifurcation of the left mainstem coronary artery, and a graft could have been inserted into the left anterior descending artery distal to the area of obliterative fibrosis. Ligation of the grafted vessels just distal to the aneurysm may be advisable in this circumstance to eliminate the possibility of embolization of the distal artery, since friable clot has been found in the aneurysm in some patients.[7,13] In one patient[9] the coronary arteriogram performed 18 months after saphenous vein graft surgery demonstrated a new aneurysmal dilatation in a coronary artery distal to the site of vein graft insertion, and there was extension of an aneurysm previously noted in a nongrafted vessel. This observation suggests a diffuse structural defect of the coronary arteries that in some patients may make a surgical approach futile as far as long-term survival is concerned.

Etiology

It is often difficult to determine the exact cause of coronary arterial aneurysm, even at autopsy. In this case we have presumed a congenital defect because of the patient's youth and the absence of other apparent cause of coronary aneurysmal formation such as penetrating chest trauma,[15] polyarteritis nodosa,[16] septicemia[14] or arteriosclerosis.[4,17] The influenza-like illness experienced by the mother during the first trimester of pregnancy is of interest, but any relation between this illness and the coronary arterial aneurysms or cleft lip is purely speculative.

Acknowledgment

We are indebted to Jesse E. Edwards, MD, Director of Laboratories, Miller Division—United Hospitals, St. Paul, Minn., for assistance in the pathologic description of the heart and for providing the photomicrographs in Figure 4.

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Aortic Origin of the Left Pulmonary Artery

Variant of Tetralogy of Fallot

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A case of tetralogy of Fallot with aortic origin of the left pulmonary artery is presented. This rare malformation should be suspected in a child with stunted growth, cyanosis, a continuous murmur over the pulmonary area and a hypervascular left lung on chest roentgenogram. Final diagnosis depends upon cardiac catheterization and angiocardiography. During surgical correction of the tetralogy, the left pulmonary artery can be divided from the aorta and anastomosed to the main pulmonary artery.

Tetralogy of Fallot with origin of the left pulmonary artery from the ascending aorta is a rare anomaly that is usually diagnosed by angiocardiography[1,2] or at autopsy.[3–5] Early recognition of this malformation is important because surgical correction may provide the only chance for survival.[2] If the anomalous origin of the left pulmonary artery is not recognized before surgery, attempts to correct the tetralogy can be disastrous.[5] Our experience with a recent case provided an opportunity to review this entity. Its association with hypoplasia of the main pulmonary artery has not previously been reported.

Case Report

A 5 month old female black infant was admitted with vomiting and diarrhea. She was slightly cyanotic; height was 58.4 cm and weight 3.8 kg (birth weight 1.8 kg). The heart rate was 120 beats/min. There was no clubbing. The peripheral pulses were normal in all four limbs. The thorax was normally shaped. No thrills were palpated. The second heart sound was single and accentuated. A grade 3/6 continuous murmur was heard over the pulmonary area.

Routine laboratory data were within normal limits. An electrocardiogram revealed sinus tachycardia, right axis deviation and right ventricular hypertrophy (Fig. 1). A chest roentgenogram demonstrated cardiomegaly, overcirculation of the left lung and distinct diminution of blood flow to the right lung (Fig. 2).

Cardiac catheterization data are shown in Table I. A right ventriculogram revealed simultaneous opacification of both a dilated aorta and a hypoplastic right pulmonary artery. There was delayed filling of the left pulmonary artery from the aorta (Fig. 3). An aortogram disclosed origin of this artery from the ascending aorta (Fig. 4).

After an uneventful hospitalization, digoxin maintenance therapy was continued. The patient remained asymptomatic until age 9 months when she was readmitted with a temperature of 104.6° F and severe cyanosis. She died 1 hour after admission. Autopsy was performed.

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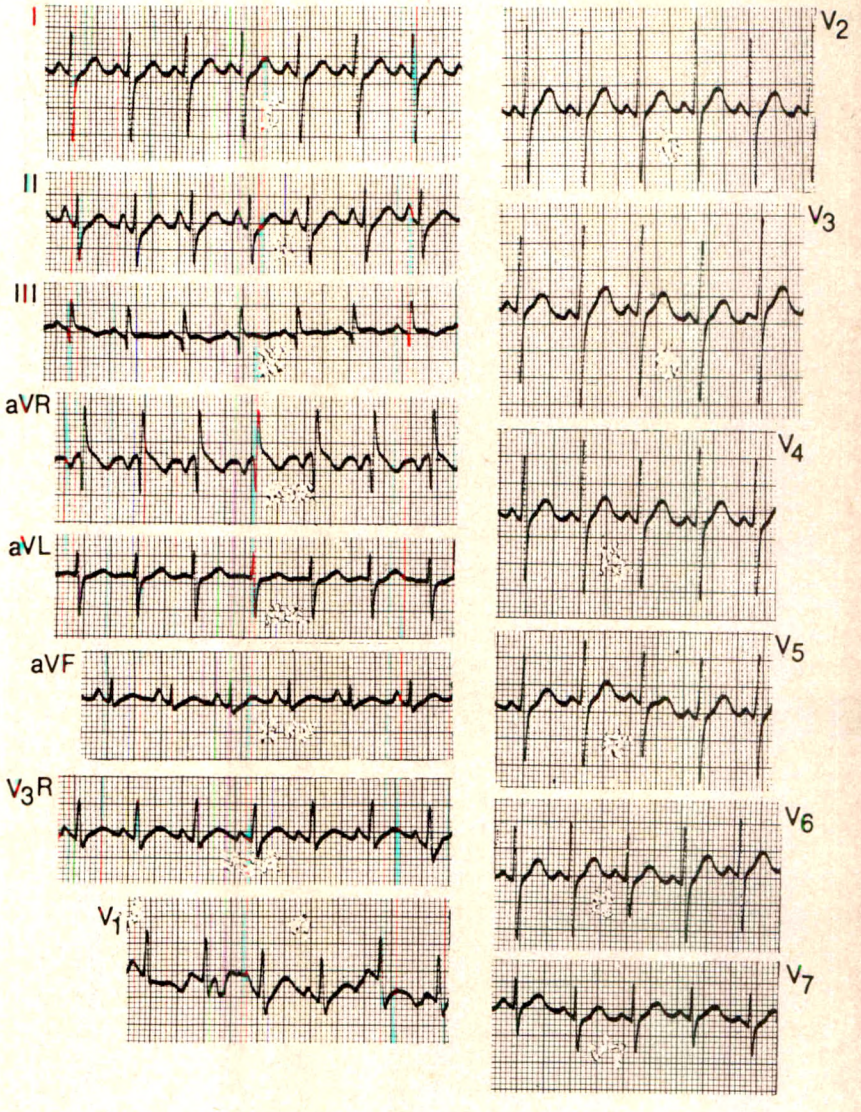

FIGURE 1. Electrocardiogram demonstrating sinus tachycardia (rate 136 beats/min), right axis deviation and right ventricular hypertrophy. The upright T waves over the right precordial leads suggest systolic overload of the right ventricle.

Autopsy Findings

Gross Anatomy of the Heart

The heart was slightly enlarged with a single arterial trunk at the base sweeping to the right and continuing as a left aortic arch with a normal branching pattern. Ten mm from its origin, a large branch originated on the left side of the aorta and continued as the left pulmonary artery. No ductus arteriosus was present (Fig. 5). The base of the right ventricle contained a 7 mm interventricular septal defect beneath the medial leaflet of the tricuspid valve. Anterior to this defect the right ventricular outflow tract communicated with a 3 mm vessel that proceeded posteriorly to the hilum of the right lung. The pulmonary valve consisted of a single flap of endothelium (Fig. 6 and 7). To the right and posterior to the hypoplastic right pulmonary artery a large aortic root, 18 mm in diameter, overlay the interventricular septal defect. At its origin were three leaflets of equal size with thickened rolled edges. The right sinus of Valsalva contained a prominent ostium that communicated with a single coronary artery. This vessel divided into a right and left branches. Other anatomic structures were within normal limits.

TABLE I

Cardiac Catheterization Data

	Oxygen Saturation (%)	Oxygen Content (vol %)	Pressure (mm Hg)
SVC	78	13.6	...
IVC	80	13.9	...
RA			
Low	80	13.9	
Mid	84	14.6	(−4)
High	82	14.3	
RV			79/3
Proximal	82	14.3	
Distal	85	14.7	
LA	95	16.5	(6)
LV	96	16.6	79/4
Aorta	85	14.7	80/60 (68)

Figures in parentheses indicate mean pressures.

IVC = inferior vena cava; LA = left atrium; LV left ventricle; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

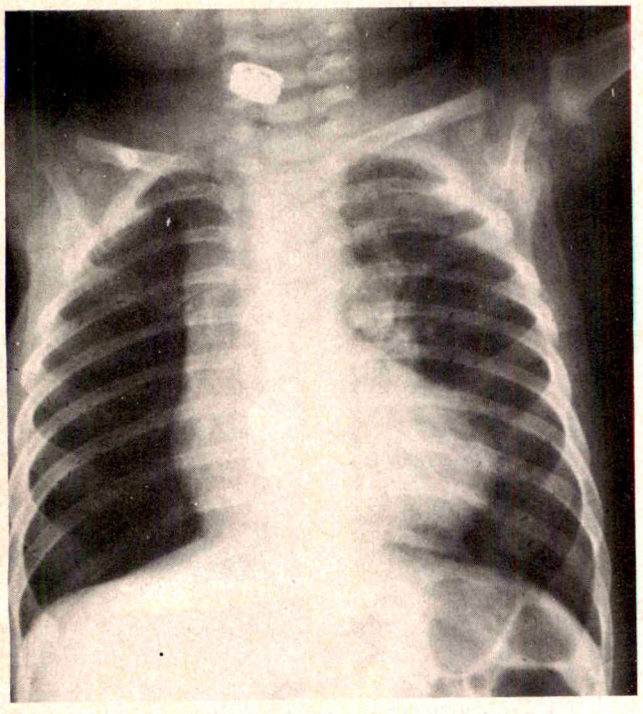

FIGURE 2. Chest roentogenogram revealing cardiomegaly, prominent central left pulmonary markings and marked decrease in blood flow to the right lung.

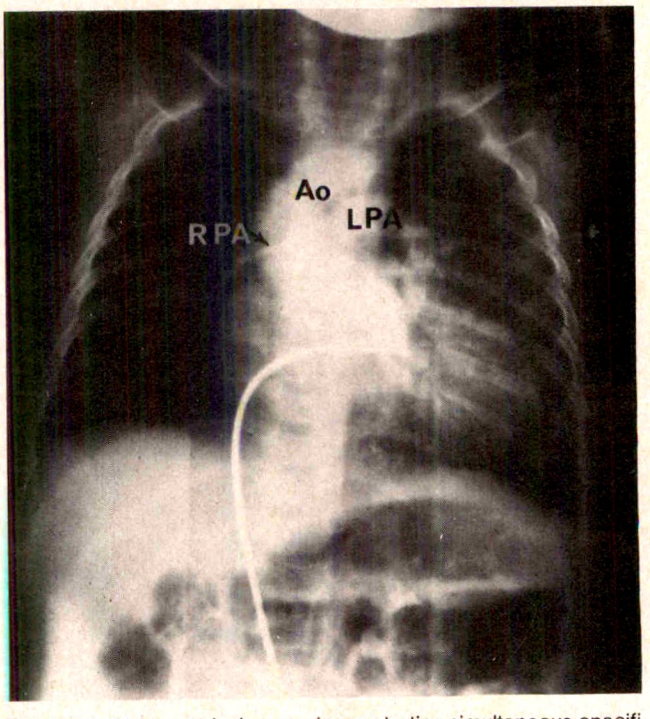

FIGURE 3. Right ventriculogram demonstrating simultaneous opacification of the aorta (Ao) and hypoplastic right pulmonary artery (RPA). The aortic trunk gives rise to the dilated left pulmonary artery (LPA). The origin of the right pulmonary artery is not clearly delineated.

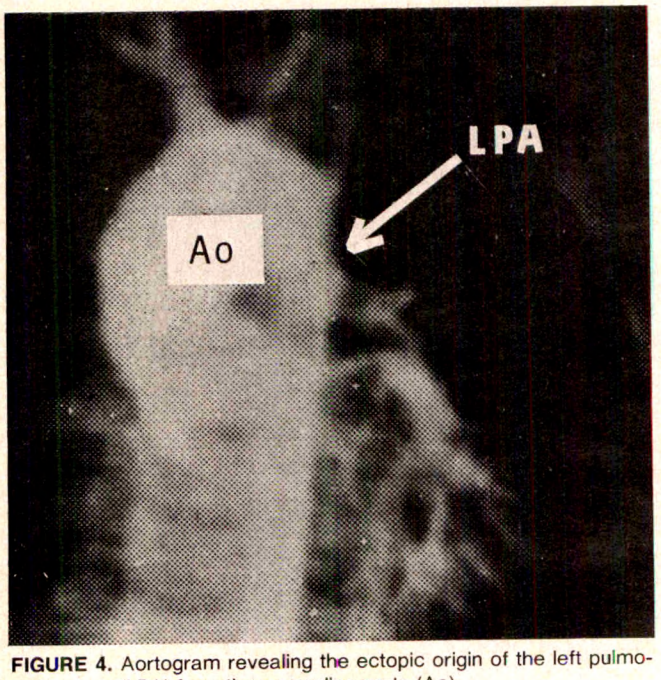

FIGURE 4. Aortogram revealing the ectopic origin of the left pulmonary artery (LPA) from the ascending aorta (Ao).

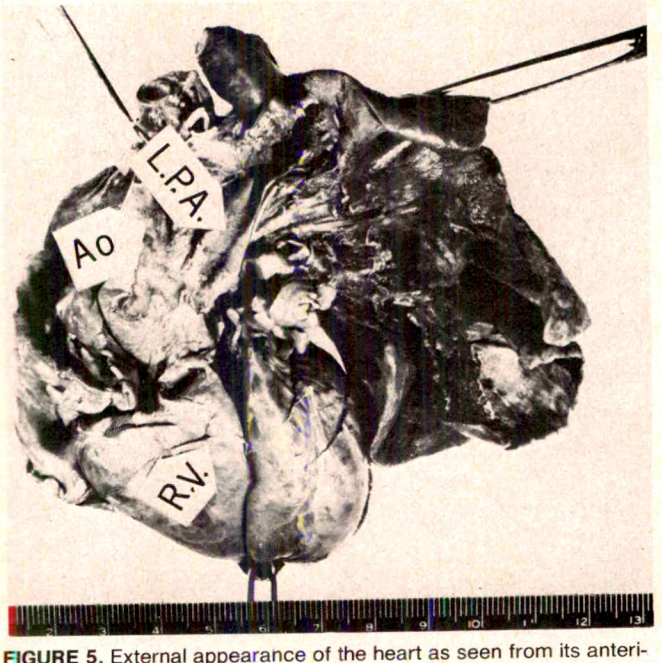

FIGURE 5. External appearance of the heart as seen from its anterior surface. A large aortic trunk (Ao) gives rise to a dilated left pulmonary artery (L.P.A.). R.V. = right ventricle.

Additional findings were hypoplastic right lung, pneumoccocal meningitis, and fatty metamorphosis of the liver.

Postnatal Cardiac Circulation: (Fig. 8)

The systemic venous return to the right atrium, right ventricle and right pulmonary artery was normal. Because of the hypoplastic right pulmonary artery and overriding aorta most of the right ventricular content was ejected into the aortic trunk.

The pulmonary venous blood returned normally to the left atrium and left ventricle. Since the mean left atrial pressure was higher than the right, there must have been a left to right shunt across the atrial septal defect. Because of the small size of this defect, the shunt was negligible as re-

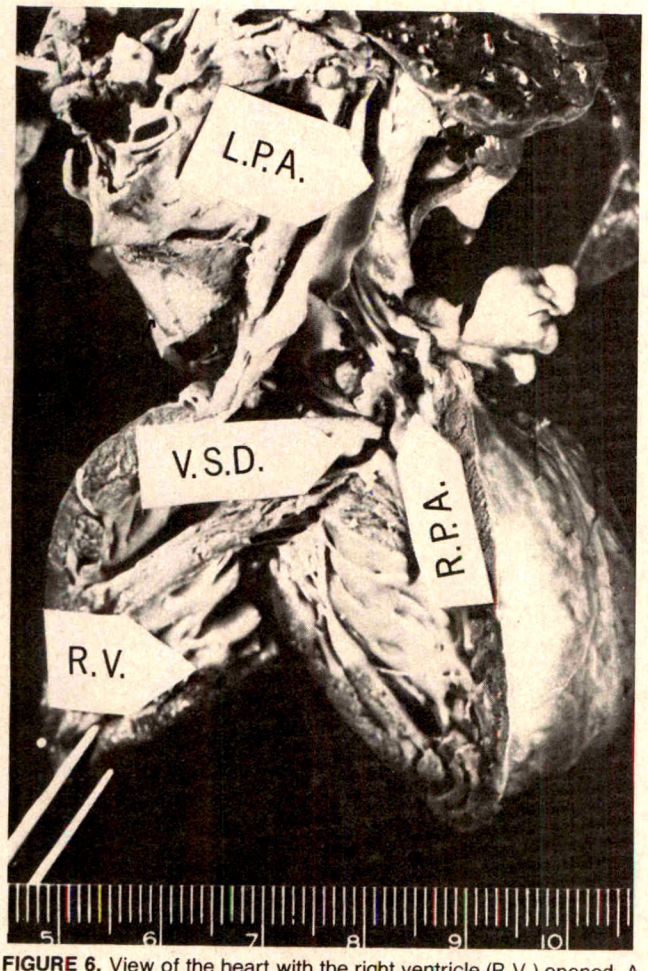

FIGURE 6. View of the heart with the right ventricle (R.V.) opened. A probe has been passed through a ventricular septal defect (V.S.D.). L.P.A. = left pulmonary artery; R.P.A. = right pulmonary artery; R.V. = right ventricle.

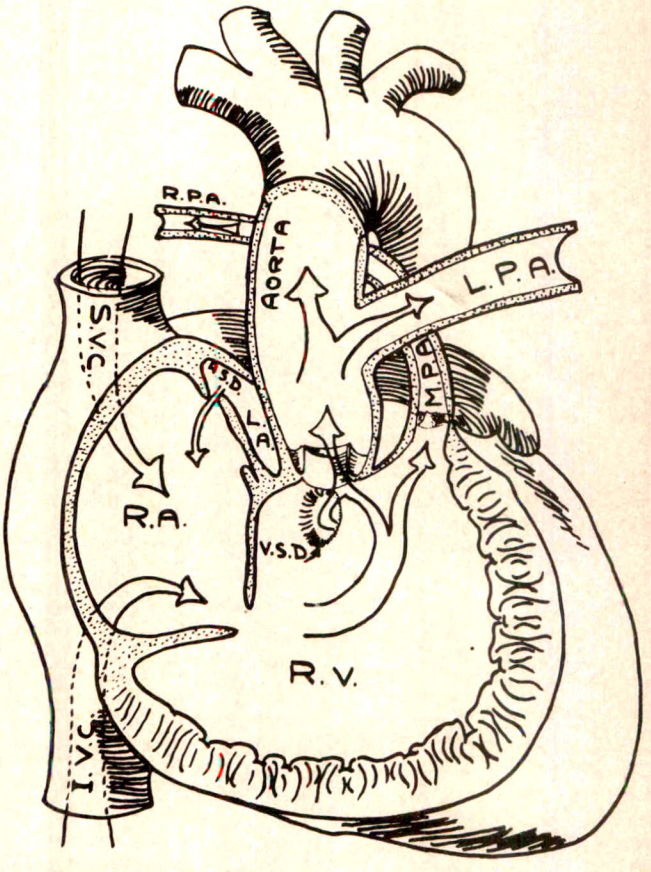

FIGURE 8. Postnatal cardiac circulation. The right ventricle (R.V.) ejects its content into the hypoplastic main (M.P.A.) and right (R.P.A.) pulmonary arteries. Left ventricular blood is ejected into the aorta through a ventricular septal defect (V.S.D.). The left pulmonary artery (L.P.A.) originates from the ascending aorta. A.S.D. = atrial septal defect; I.V.C. = inferior vena cava; L.A. = left atrium; R.A. = right atrium; S.V.C. = superior vena cava.

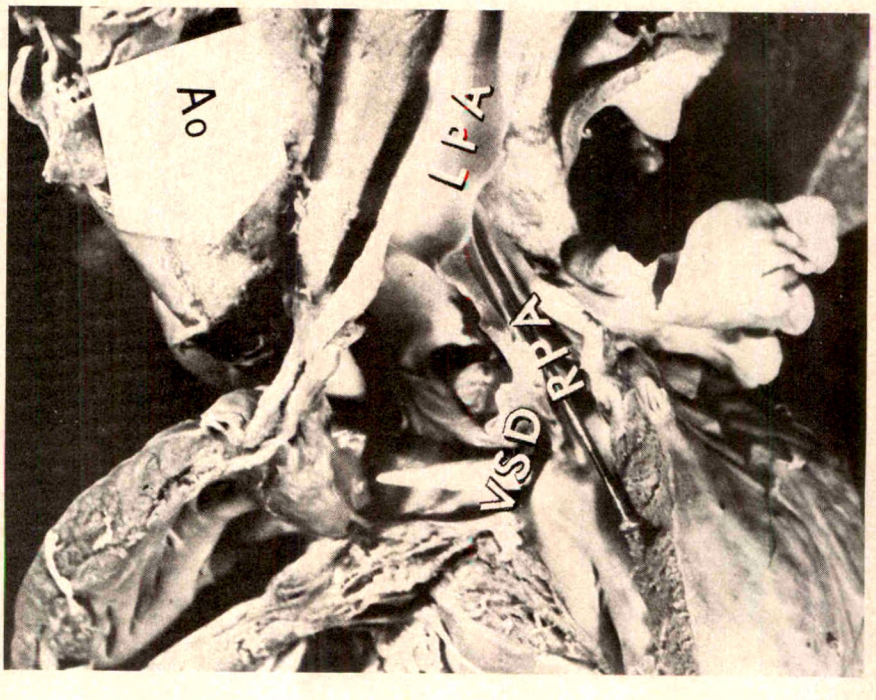

FIGURE 7. Base of the heart as seen from the right ventricle. A probe has been passed through a ventricular septal defect (VSD). A pin has been placed into a hypoplastic right pulmonary artery (RPA). The aorta (Ao) overrides the ventricular septal defect (VSD) and gives rise to a large left pulmonary artery (LPA).

TABLE II

Summary of Seven Cases

Case no.	Author & Year	Age & Sex	Clinical History	Physical Signs	Chest Roentgenogram	Electrocardiogram	Cardiac Catheterization & Angiocardiography	Outcome
1	Thomas[3] (1941)	3 mo, F	Dyspnea, cyanosis	Continuous murmur	...	...	...	Died of bronchopneumonia at 3 mo
2	Sikl[4] (1952)	Stillborn M	...	...	...	...	...	Stillborn
3	Mudd et al.[1] (1964)	1 yr, M	Slow growth; cyanosis	Murmur	Cardiomegaly; increased left pulmonary vascularity	Right ventricular hypertrophy	Yes	Loss to follow-up at 4 yr
4	Czarnecki et al.[5] (1964)	4 yr, F	Slow growth; cyanosis	Clubbing; S_2 single and normal intensity; continuous murmur; normal pulses	Normal heart size and pulmonary vascularity	Right atrial and right ventricular hypertrophy	Yes	Died during repair of tetralogy
5	Morgan[2] (1972)	20 mo, F	Cyanotic episodes	S_2 single and accentuated; continuous murmur	Cardiomegaly; increased left pulmonary vascularity	Right ventricular hypertrophy	Yes	Total correction; doing well at 29 mo
6	Kirklin et al.[8] (1965)	...	...	...	...	...	...	Total correction
7	Current case	5 mo, F	Vomiting; diarrhea; slow growth; cyanosis	S_2 single and accentuated; continuous murmur; normal pulses	Cardiomegaly; increased left pulmonary vascularity	Right ventricular hypertrophy	Yes	Died of pneumococcal meningitis at 9 mo

flected by the absence of an increase in right atrial oxygen saturation (Table I). The left ventricle emptied its contents through the interventricular septal defect into the aorta. The mixing of right and left ventricular blood resulted in decreased oxygen saturation in the arterial vascular bed. This was evidenced by an oxygen saturation level of 85 percent in the aorta (Table I). The left pulmonary artery was totally supplied by the aorta.

Discussion

Clinical Features

Enough data are available in six reported cases (and our own) to permit clinical analysis (Table II).

In four female and two male patients a cardiac problem was suspected before the age of 1 year. Clinical history included retardation of growth (Cases 3, 4, and 7), cyanosis (Cases 1, 3 to 5 and 7) and cyanotic episodes (Case 5). No patient had congestive heart failure.

Clubbing was present in one patient (Case 4).

The second heart sound was single in three cases (Cases 4, 5 and 7), normal in intensity in one (Case 4) and accentuated in two (Cases 5 and 7). A continuous murmur was heard over the pulmonary area in four patients (Cases 1, 4, 5 and 7); peripheral pulses were normal in two (Cases 4 and 7).

Chest roentgenograms revealed a hypervascular left lung in addition to cardiomegaly (Cases 3, 5 and 7). In one case pulmonary vascularity was normal (Case 4).

Electrocardiograms demonstrated right atrial hypertrophy (Case 4), and right ventricular hypertrophy (Cases 3 to 5 and 7).

Angiocardiography was essential to confirm the diagnosis (Cases 3, 5 and 7). In only one patient (Case 4) was the ectopic origin of the left pulmonary artery not recognized after angiographic studies. The right ventriculogram revealed simultaneous filling of the right pulmonary artery and ascending aorta and late opacification of the left pulmonary artery. The ascending aortogram demonstrate the ectopic origin of the left pulmonary artery.

Anamolous origin of the left pulmonary artery from the ascending aorta may occur without tetralogy of Fallot[6,7] and also give rise to hypervascularity of the left lung. But, in contrast to tetralogy of Fallot with origin of the left pulmonary artery from the aorta, the condition is associated with a right aortic arch and congestive heart failure.

In conclusion, the clinical findings are characterized by retardation of growth, cyanosis and a continuous murmur over the pulmonary area. Chest roentgenograms reveal an enlarged heart and overcirculation of the left lung. The electrocardiogram usually reveals right ventricular hypertrophy. This combination of findings does not provide a definite diagnosis but should alert the physician to the need for cardiac catheterization and angiocardiographic studies.

Surgery

Successful anastomosis of the ectopic left pulmonary artery to the main pulmonary artery has been reported in cases without[6,7] and with[2,8] tetralogy of Fallot. In the latter group, the anastomosis can be performed during total correction of the tetralogy. If the anomalous pulmonary artery is not recognized before surgery, repair of the tetralogy may result in severe bleeding and death of the patient.[5] Since progressive hypertensive vascular changes can develop in the left lung when the pulmonary artery arises from the aorta,[7] complete surgical correction is advisable at an early age.

Acknowledgment

We express our gratitude to Dr. Jesse Edwards for his excellent advice in reviewing this manuscript.

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Prevention of Heart Disease by Control of Risk Factors: The Time Has Come to Face the Facts

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This editorial might seem unappreciative of the thousands of man hours and years of laborious, laudable investigations in the field of arteriosclerosis. If this is the case, we apologize, for at this time we are principally searching for conclusive facts that can be used in planning for the nation's health. Through the years we have become aware that segments of research information have often been pulled together prematurely and the population propagandized into believing that the problem of arteriosclerosis has been conquered. Possibly these tactics were used to motivate Americans to practice a more prudent way of life. But we are alarmed that some national health planners have indicated that there is no need for more research on arteriosclerosis, that if a few simple rules for risk factor intervention are followed, a health problem that kills more than 1 million Americans each year will disappear.

Recently there have been several challenges to the view that correcting risk factors will prevent, retard or reverse coronary arteriosclerosis.[1–4] A principal architect of the Framingham study, which established coronary risk factors, has declared:[1] "There are few prophylactic measures of proved efficacy in coronary heart disease. This applies to primary and secondary prevention. Neither hygienic, pharmacologic nor surgical measures have been shown conclusively to delay acute episodes or to prolong life."

A recent editorial in *Lancet*[2] casts this doubt: "So far, despite all the effort and money that have been spent, the evidence that eliminating risk factors will eliminate heart disease adds up to little more than zero in terms of preventing heart disease on a public health scale." And the Food and Drug Administration has, in effect, formalized these doubts by demanding that advertisements for certain lipid-reducing drugs carry this qualifying codicil: "Important Note: It has not been established whether drug-induced lowering of serum cholesterol and other lipid levels has a detrimental, a beneficial, or no effect on morbidity or mortality due to atherosclerosis or coronary heart disease."

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The three statements suggest that we need to be reminded of the extensive report on arteriosclerosis released in 1971 by the National Heart and Lung Institute.[4] It was the result of a year-long deliberation by a blue ribbon task force of 102 scientists. It evaluated the currently available information on arteriosclerosis and formulated recommendations and long-range programs. It cast doubt on many beliefs now accepted as gospel. We believe it implied that we do not understand the basic mechanisms underlying development of the arteriosclerotic lesion, nor how various risk factors bring about development of clinical disease, and that the major means of preventing and treating heart disease have yet to be elucidated. Unfortunately, the report was not widely circulated.

It should be said here that we believe there is considerable validity to the risk factor hypothesis. However, the report of the National Heart and Lung Institute indicates that we must question whether reduction of these factors will (1) stop progression of arteriosclerotic lesions in the majority of patients, or (2) reverse the lesions once they become manifest. Our meticulous study of that report on arteriosclerosis suggests that scientists are laboring in research ruts indelibly cut by countless man years of investigations and stimulated by statistical associations. We conclude that some risk factors have been demonstrated both retrospectively and prospectively to be associated with a higher incidence of arteriosclerotic lesions and that these associations are probably valid. However, some appear to be trivial or weak secondary associations, and others are a grouping of symptoms that reflect more basic underlying causes such as social behavior problems, genetics or systemic disease processes.

One Hundred Years of Lipid Infiltration Hypothesis

In 1862, Virchow postulated lipid infiltration as the cause of atherosclerotic lesions, and this hypothesis was fortified by Anitschkow, who in 1913 demonstrated that a diet with unnaturally high cholesterol levels can induce atherosclerosis in rabbits, and that correction of the diet can cause the lesions to regress. Many of the subsequent dietary recommendations on lipids were based on experimental findings in animals

given diets to which the species is not naturally accustomed. Extrapolation of these data to human beings must assume a diet that has been modified over the years to an equally toxic level.

The conclusions derived from animal studies can be challenged on many other grounds. Altschule[3] concluded: "Any real proof of a relation between cholesterol and fat dietary control on the one hand, and blood cholesterol levels and heart disease on the other, is yet to be established."

There is undoubtedly an entity of familial arteriosclerosis, attributable to genetic hyperlipoproteinemia, that might be benefited by a lipid-reducing diet and drugs. But this entity accounts for only 1 to 5 percent of the overall population with arteriosclerosis. On the other hand, hyperlipidemia is not always associated with arteriosclerotic lesions. For example, patients with chronic rheumatic heart disease with very high blood cholesterol levels resulting from induced myxedema underwent autopsy years later and were found to have coronary arteries free of atherosclerosis.[5] Possibly too much emphasis has been placed on lipids as a cause of atherosclerosis; only about 20 percent of patients admitted to a coronary care unit have an "abnormal" serum lipid profile. However, in all fairness lipid values now considered "normal" might actually be high, for within the usual range of cholesterol values there is a five-fold range of risk proportional to the level.

The *Lancet* editorial[2] concluded: "A key test is to show that electively reducing serum-cholesterol reduces clinical atherosclerotic cardiovascular disease. The evidence in man is hopeful, but miniscule in comparison with the general aura of faith in such therapy." Kannel[1] has stated: "There is as yet no confirmed efficacy in lowering blood lipids."

Epidemiologic Surveys

The Framingham study, a classic investigation that helped elucidate the precursors of coronary disease, was instituted 25 years ago by a group of tough-minded scientists including Mountin, Dawber and Kannel. It indicated that elevated levels of serum lipids, including cholesterol, phospholipids, beta and prebeta lipoproteins; hypertension; obesity; low vital capacity; electrocardiographic abnormalities, including left ventricular hypertrophy, intraventricular block and atrial fibrillation; diabetes; genetic disposition; smoking; and a sedentary life style were all associated with an increased incidence of coronary disease.[6] The findings have been corroborated by others.

At the same time there appeared to be an increasing incidence of coronary disease, and it was promulgated that an epidemic was occurring in many countries. Concurrently, public hygiene improved and antibiotic agents were developed that increased the life expectancy of the American population considerably until the year 1960. Between 1960 and 1968 life expectancy remained relatively the same because of the rising incidenc of our two main killers, arteriosclerotic heart disease and cancer. This rise in mortality from heart disease should be attributed not solely to a change in life style, but also to the fact that people are now living into the age group in which pathologic lesions and symptoms of arteriosclerosis become clinically evident. This was brought to our attention during a recent visit to China. The late Isadore Snapper had taught us that in 1940 arteriosclerosis was not a clinical problem in China because the Chinese ate a nonatherogenic diet. We now learn that there is a high incidence of coronary disease. When we asked our hosts what had happened, they explained that the type of diet has not changed, but that life expectancy was less than 33 years at the time Snapper lived in China, and now the population survives to an average age of 56 years.

Since 1968 there appears to have been a moderate reduction in deaths from heart attacks in the United States, but the evidence is not conclusive. This possible reduction may be related to public awareness to seek earlier care and the implementation of modern coronary care concepts and other emergency services.

Other Coronary Risk Factors

Hypertension: The Framingham studies showed a strong association between hypertension and arteriosclerosis,[6] and a recent Veterans Administration study[7] revealed that proper control of hypertension can reduce the incidence of cerebral stroke. But this study did not provide a population sufficiently large or young to prove that correction of hypertension will reduce the incidence of coronary occlusion once it is clinically established. Such proof may emerge from the current 14 center-10,500 subject cooperative hypertension study of the National Heart and Lung Institute. However, we are perplexed by a report[9] of a randomized cooperative study in which antihypertensive therapy after a stroke appeared to offer 452 patients with moderate hypertension little benefit in the rate of stroke recurrence or time of survival during an average follow-up period of 3 years.

Exercise: Exercise faddists have published studies claiming that those who live a sedentary life could prevent and even reverse arteriosclerotic lesions by engaging in vigorous exercise habits. This view is questioned by the National Heart and Lung Institute report,[4] which states: "The idea that regular physical exercise decreases the danger of death or disability from coronary atherosclerotic disease is based on a number of assumptions, some proven and some of questionable validity. . . . But there is no convincing data to indicate that exercise will, in fact, decrease either the rate of development of atherosclerosis, or prevent its complications."

Tobacco: Tobacco has been strongly incriminated as a risk factor, but no direct proof has been provided to show that cigarettes are atherogenic. We must question if the increased risk is really due to tobacco because it has been suggested smoking represents a personality disorder that itself may contribute to the arteriosclerotic process.

Scientists have implicated a rise in serum lipid lev-

els with cigarette smoking as a possible cause of arteriosclerosis. However, this assumption appears to be questioned by the statement[4]: "The possibility that cigarette smoking raises the levels of blood lipids deserves further study, although present evidence is that the correlation between smoking and serum lipid levels is of a low order." Convincing evidence has also been reported that cigarette smoking triggers cardiovascular events such as catecholamine release and sudden death. We wonder why toxicologists have not concentrated on the effects of burning chemically treated cigarette paper because, when paper and tobacco are incinerated separately, the paper causes the most severe irritative phenomena such as lacrimation and coughing.

Obesity and diabetes: The arteriosclerotic lesions might be due not to obesity as such but to two complications of obesity, diabetes and hypertension. The National Heart and Lung Institute report[4] states: "There is disagreement as to the extent of coronary disease in obese individuals without either hypertension or diabetes; most studies have shown a modest excess of coronary disease in those who are overweight."

Diabetes has been strongly incriminated as a risk factor. But it is difficult to implicate the associated hyperglycemia itself because, although blood sugar levels may be well controlled in the diabetic patient, the arteriosclerotic process may continue to advance. Probably some undisclosed diabetic factor causes the premature atherosclerosis.

Genetic factors: It is evident that heredity is a most important factor in the ideology of arteriosclerosis. New fields of study might provide a major breakthrough to control the baffling genetic problem.

The Need to Test Multifactoral Risk Factors

At present, there is no conclusive evidence that preventive measures based on correction of single risk factors will prevent arteriosclerotic heart disease. The National Heart and Lung Institute report[4] appears to challenge present concepts: "Despite evidence that combinations of risk factors increase the risk of arteriosclerosis and its complications there is, as yet, no conclusive evidence that intervention with respect to normalizing these risk factors will reduce the risk of arteriosclerosis. Not all investigators share this confidence in the primary pathogenic role of the risk factors that have been identified to date and a lowering of risk by multiple intervention would provide proof of the risk factor hypothesis."

To test the multiple risk factor hypothesis, the Institute has begun a comprehensive program to recruit approximately 12,000 male volunteers, aged 35 to 54 years, whose blood pressure levels, cholesterol levels and smoking habits, alone or in combination, place then at higher risk than the general population. The volunteers are to be divided into two groups. One group will be assigned to special intervention programs, the goals of which will be to reduce blood cholesterol level by 10 percent, bring blood pressure down to normal, and reduce or eliminate cigarette smoking. The other group will be given no special treatment but will remain under the care of a physician and appear annually for a checkup. At the end of 6 years, the answer will probably be obtained as to whether multiple risk factor intervention will reduce the incidence of first heart attack and deaths from coronary artery disease.

Should Risk Factor Intervention Be Commenced Early in Life?

Intimal thickening of the coronary arteries may begin before birth and incubates progressively through a latent period until it produces clinical manifestations in middle age. It is believed that once the changes produce clinical manifestations they cannot be reversed.[10] Therefore, if methods are developed to affect the course of the lesions, they should be applied as preventive measures in the pediatric age group.

On the premise that lipids play a role in either the origin or the extension of fatty streaks, alteration of fat intake has been the major dietary change proposed. In instances of familial type II hyperlipoproteinemia, control of dietary factors has been emphasized. It is now evident that benefits of large-scale dietary alterations are unproved and risks are unknown. For instance, the use of fat-free milk has been challenged because dietary practices that cause relative hypocholesterolemia during the first few months of life may lead to abnormal development of the brain and nervous system.[11] The real question is whether a cholesterolgenic diet is harmful to all Americans or to a limited number of clinically discernible groups. Because florid hyperlipoproteinemia accounts for less than 5 percent of all coronary heart disease, before massive intervention is attempted further studies should be implemented to determine whether measures to improve the diet of infants are safe, and whether long-term dietary change has the potential for causing harm. Possibly for the present it would be advisable to identify and treat the 1 to 5 percent of American children destined to have clinical atherosclerosis, rather than to tamper with the diets of the great majority. Until we know more, perhaps lipoprotein typing should be an integral part of the routine evaluation of infants and young adults who have a threatening family history.

Should We Practice Interim Risk Factor Control in the Adult Population?

What should the doubting profession advise the patient? We agree with Kannel,[1] who stated: "Until more data on the efficacy of preventive measures becomes available, the practicing physician must decide for himself whether sufficient rationale for intervention exists. He must weigh the hazards against the potential benefits. . . . If he elects to proceed on the incomplete evidence available, he can take comfort in the fact that the measures advocated are good health practices and have other benefits. Who can seriously

argue with the general merit of a program that advocates maintenance of lean body weight, a less rich diet, physical fitness, giving up cigarettes, and control of hypertension, diabetes, and hyperlipidemia." Most physicians agree that there is no harm in advising the patient to follow a prudent diet and life style. But in this age of informed consent we must inquire if the practitioner should explain to each patient that risk factor interventions are not yet conclusively proved and might not be effective.

Appraisal

Most investigators agree that the risk factor hypothesis has provided valuable information and to be successful must be applied well before clinical evidence becomes manifest. But once arteriosclerosis is clinically evident, there is little evidence the lesion can be reversed.

Within a decade we should learn the results of National Health and Lung Institute studies of reducing lipids in certain lipid disorders and of controlling hypertension; we should also have data on the promising possibility that control of a combination of three major risk factors may affect the course of coronary disease. If risk factor interventions prove successful, and if these measures were then applied to the entire population it would appear that at best only about 5 to 20 percent of cases could be controlled. If intervention trials were implemented to control risk in the genetically prone high-risk offspring in infancy, possible benefits would not be learned until that population reached the age of clinical manifestations, 50 to 65 years later.

These considerations suggest an urgent need for new fundamental research and reappraisal of existing experimental and clinical studies, including national population research. Perhaps future studies should investigate in man immunologic and other factors that cause accelerated obstruction of the transplanted veins used in coronary or femoral bypass surgery, and galloping atherosclerosis in the transplanted heart. Such transplanted tissue could provide valuable models for intervention trials. Repeat arteriograms of obstructive lesions in patients who are progressing through exacerbations and remissions of cachexic illness might also provide an excellent model. We postulate that future investigations will elucidate many other types of arteriosclerosis and each will require a specific form of therapy.

Imaginative investigators might well look for other likely causes of arteriosclerosis that, when identified, could be investigated thoroughly by a disciplined program managed by leading scientists of the world brought together in specialized centers. Such programs could be fashioned and financed with the same sense of urgency with which our nation dramatically pursued the atomic energy, missile and space programs. However, these successful efforts were perhaps better supplied with the basic information necessary to formulate and execute a productive program. In physics, for instance, it was Einstein's famous equation $E = mc^2$ that provided a major step toward the development of nuclear energy. As yet, we do not appear to possess a formula for the basic genesis of the arteriosclerotic lesion and its prevention because we do not understand the basic underlying mechanisms or how various risk factors influence the progress of the lesion to bring about clinical disease.[4] This lack of knowledge makes it difficult to provide rational programs for prevention and treatment. In the meantime we must follow the pragmatic approach, which often resembles empiricism.

If the multiple risk factor trials fail to prevent the progress of arteriosclerosis, health planners may be reduced to a state of scientific bankruptcy. In planning the defense of a country, the military plan for all future eventualities, including possible failure; the scientific community should also have plans under way in case multiple risk factor trials fail to provide a defense against the nation's biggest killer.

It appears that our nation's overconfidence in present risk factor concepts is impeding development of other promising preventive approaches. Because it will take years to dislocate and relocate the human resources for a new major multidisciplinary attack on the problem of arteriosclerosis, we plead that our Congress provide the highest priority of funding to encourage a more massive research attack now. And we ask again: Where are the alternate plans for defense against our nation's biggest killer?

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President's Page: Solving Our Own Problems

This is the last President's Page I shall write. It has been my privilege to lead the College for a year. It is time for new leadership . . . new ideas. These will be afforded by our new President, Charles Fisch, MD, FACC.

In my first Page in the March issue of this Journal I wrote, ". . . one cannot help but be a bit concerned for the future. The year 1973 has seen the overwhelming vote of confidence of our national leadership vanish with the resignation of the Vice-President, who preferred not to contest the truthfulness of charges; the evidence that power might well have been ruthlessly used for no other purpose than acquiring more power; the decline of confidence in our chief executive on the domestic front despite rather remarkable accomplishments in some sectors of the international front. 1973 was a year in which the social and the political fiber of our country was stretched to and beyond the breaking point. If this was not enough, as a nation we were forced to recognize that we were no longer the master of our economy but that our pursestrings could be controlled by others if for no other reason than military gain. These and other events prompted Jack Anderson to report in his syndicated column of January 1, 1974, 'There is a strong feeling that it is up to the American people to bail the country out of its difficulties because the leadership in government cannot do it.' "

In succeeding Pages I have focused attention on a variety of subjects. But always I have tried to emphasize the role of physicians, the members of the American College of Cardiology, as leaders in the community, the nation and the world. I closed that first letter in March 1974 with a quotation from William Allen White, "I am not afraid of tomorrow, for I have seen yesterday and I am in love with today."

Joseph Alsop wrote in his column on December 3, 1974, "I have been asking myself again and again what has been the greatest change to come to the United States in my modestly long lifetime? Somehow, self-confidence and energy have been replaced by fear and impotence . . . and this in a nation grown far more numerous, far richer and far more powerful than the long ago America of my youth." Alsop recalled the great depression, the period when "great numbers of Americans were fearful and felt helpless." That was before 1933, before the admonition that we had "nothing to fear but fear itself." Alsop reminded the reader that from the depth of the despair of those days the recovery in the "thirties was far from instantaneously or overwhelmingly successful. But America in those days was a country whose people firmly believed that they could always solve their own problems . . . it is that belief," Alsop concluded, "that is so largely lost. I still wonder why."

Why have we not seen the doctors, the members of the American College of Cardiology, rise up with confidence for the future? Is it that we have grown comfortable in our own way of life and put blinders on so as to be able to ignore the questionable in our own environment for fear that we may have to change, and that change makes us uncomfortable?

We cannot expect to influence others until we, as a profession, have our own house in order. And in what areas is there disorder? The first is in the area of geographic and specialty maldistribution. In a recent address at the Yale University Medical Center, Senator Edward Kennedy reported that in South Dakota, each physician serves 1,400 people; in Mississippi, he serves 1,339 people; in Connecticut, 602 people. Specialty maldistribution has compounded the problems of geographic maldistribution. Specialists are more poorly distributed than primary care physicians. There are more neurosurgeons in Massachusetts for a population of 5 million people than there are in England and Wales for a population of 50 million. There are twice as many surgeons in proportion to population in the United States as in England and Wales; and Kennedy pointed out they do twice as many operations. It is possible that twice as many operations are needed and, if they are, we should be able to justify them by improved function, reduced morbidity and delayed mortality of the patient. But surgery without such evidence can hardly be justified.

I am pleased that the American College of Cardiology has undertaken a manpower study to define the number and distribution of cardiologists and, as part of the Annual Meeting, will sponsor a symposium for all directors of adult cardiology training programs on February 9, 1975, in Houston, Texas. The symposium will be entitled "Responsible Leadership in the Training of Cardiologists of Tomorrow." This problem, manpower maldistribution, requires the cooperative effort of all. It cannot be solved by the individual physician, and it cannot be solved overnight, but solutions must be found.

The second problem, that of escalating costs of health care, can be actively approached by the individual physician. With the cost of medical care continuing to accelerate, with the ability to spend enormous sums of money on hospitalization, diagnosis and therapy, there can be little doubt that restraints will have to be imposed. Will these restraints be imposed from outside the profession, or will the profession really look at what is happening . . . and do something about it? Senator Kennedy stated in his address at Yale: "I think we need to devel-

op the core of excellence in the nation for basic health services and policy research as we have for clinical and biomedical research. I am asking you to study the factors that lead to overuse of hospital beds; to the needless and irrational use of prescription drugs; to the excessive and unnecessary use of costly diagnostic tests. These are just a few examples . . . studying them would not require abandoning your standards of excellence . . . but only meeting those standards in new disciplines." This the physician can initiate within his own practice and within his own hospital. As a profession, we cannot influence our community, our nation, or the world if we do not have our own house in order. We cannot help "bail the country out of the difficulties" if we cannot solve our own difficulties.

On December 3, 1974, Joseph Alsop wrote, "America in those days was a country whose people firmly believed they could always solve their own problems . . . it is this belief that is so largely lost. I still wonder why."

Justice Learned Hand wrote, "A society in which men recognize no check on their freedom soon becomes a society in which freedom is a possession of a savage few."

1975 will be a year of greater challenges and greater decisions. The College will have greater opportunities and greater responsibilities. Your President, Dr. Charles Fisch, of Indianapolis, needs your support. Your Past President thanks you for your support and optimistically faces with you the challenges of tomorrow.

Henry D. McIntosh, MD, FACC
President
American College of Cardiology

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and various other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education in the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

FEB. 10–13 **Twenty-Fourth Annual Scientific Session.** Henry D. McIntosh, FACC, president. Albert Thomas Convention and Exhibit Complex, Houston, Texas.

MAR. 6–8 **Cardiovascular Disease—1975: Practical Diagnosis and Management.** John Ross, Jr., FACC, Robert A. O'Rourke, FACC, Joel S. Karliner, FACC and Kirk L. Peterson, FACC, directors. Sheraton Harbor Island Hotel, San Diego, Calif.

MAR. 13–14 **Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** James S. Forrester, H. J. C. Swan, FACC and Kenneth I. Shine, directors. Cedars of Lebanon Hospital, Los Angeles, Calif.

MAR. 17–20 **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. The Children's Hospital, Children's Hospital Medical Center, Cincinnati, Ohio.

MAR. 24–28 **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

APR. 7–16 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Sante Fe Inn, Rancho Sante Fe, Calif.

APR. 14–18 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Richard Gorlin, FACC, Michael V. Herman, FACC and Louis E. Teichholz, co-directors. Mount Sinai Medical Center, New York, N.Y.

APR. 16–18 **Echocardiography for the Clinician.** Joseph K. Perloff, FACC, Nathaniel Reichek and Morris N. Kotler, FACC, directors. The University of Pennsylvania Medical Center, Philadelphia, Pa.

APR. 22–24 **Optimal Standards of Care in Cardiac Emergencies.** Albert N. Brest, FACC, director. Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa.

APR. 30 to MAY 2 — **Core Curriculum: Vectorcardiography: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

MAY 5–8 — **Current Concepts in Cardiology—1975.** Philip R. Akre, director and Masato Takahashi, FACC and John A. Bowers, co-directors, Caesars Palace, Las Vegas, Nev.

MAY 10–11 — **Core Curriculum: Clinical Vectorcardiography 1975.** Irwin Hoffman, FACC and Robert I. Hamby, FACC, directors. Americana Hotel, New York, N.Y.

MAY 12–15 — **Cardiology for the Internist.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 16–18 — **Core Curriculum: Myocardial Biology in Health and Disease—1975.** Arnold Schwartz, FACC and Mark L. Entman, directors. Holiday Inn-Medical Center, Houston, Tex.

MAY 29–31 — **Ischemic Heart Disease: A Critical Overview.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Golden Gateway Holiday Inn, San Francisco, Calif.

JUNE 4–7 — **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

JUNE 5–7 — **Progress in Coronary Artery and Valvular Heart Disease.** S. H. Rahimtoola, FACC, director. University of Oregon Medical School, Portland, Ore.

AUG. 23–25 — **Tutorials in the Tetons (Cardiac Emergencies).** Robert S. Eliot, FACC, director and Robert J. Davis, FACC, Alan D. Forker, FACC and Vincent F. Miscia, FACC, co-directors. Jackson Lake Lodge, Jackson Hole, Wyo.

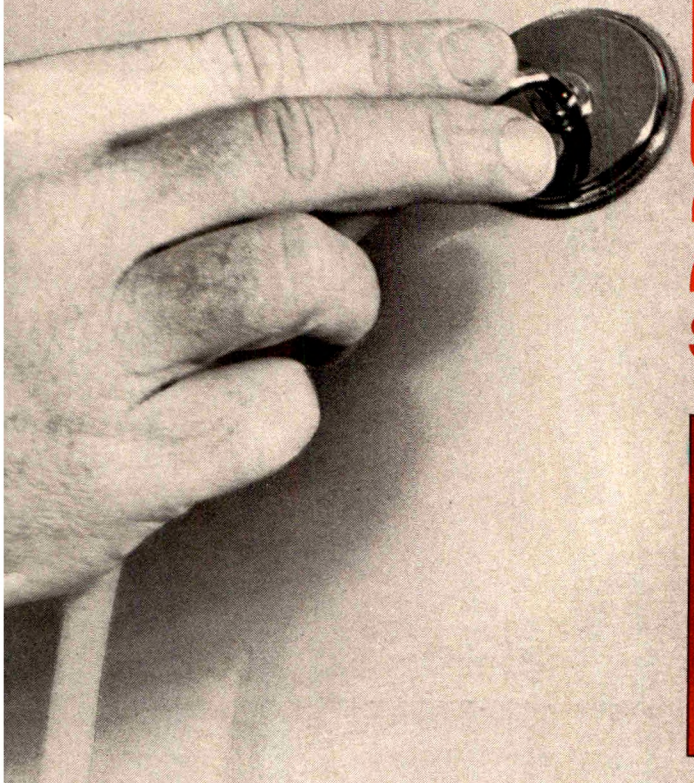
Examination in Subspecialty Area of Cardiovascular Disease

The examination of the American Board of Internal Medicine in the Subspecialty Area of Cardiovascular Disease will be administered on Tuesday, October 21, 1975. Registration begins January 1 and ends March 15, 1975. For information and application forms please write to: American Board of Internal Medicine, 3930 Chestnut St., Philadelphia, Pa. 19104.

Accepted Concepts in Angina Therapy*

- Nitrates are the first line of defense against angina pectoris
- The therapeutic goal of oral nitrate therapy is an angina-free patient

Because higher dosage often is necessary to achieve this goal...IVES LABORATORIES INTRODUCES



ISORDIL®
(isosorbide dinitrate)
20 mg.

Scored, oral tablets

Fewer tablets for patients on 80 mg. or more per day (up to a maximum of 120 mg./day)

- To provide prophylaxis against anginal attacks often caused by unavoidable everyday stress.
- To reduce the frequency and severity of angina pectoris attacks. (Not intended to abort the acute episode.)

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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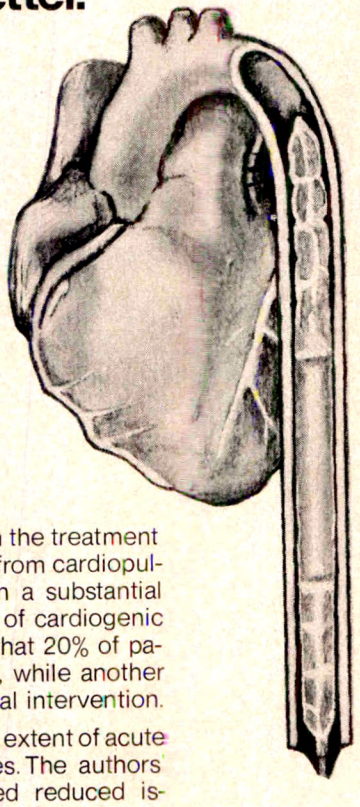
New York, New York 10017

DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

"a life-saving measure in a substantial minority of patients"[1]

The Avco Intra-Aortic Balloon Pump* ...and the Sooner, the Better.

The rationale of intra-aortic balloon pump (IABP) therapy in low-cardiac output conditions is widely accepted. By lowering pressure in the proximal aorta at the beginning of systole, myocardial work load is lessened. Also, by augmenting pressure during early diastole, pumping improves coronary perfusion and can open dormant collaterals. Thus a better balance between myocardial oxygen demand and consumption is obtained.



Documented effectiveness

The IABP's effectiveness is clinically proven in the treatment of cardiogenic shock and in weaning patients from cardiopulmonary bypass. It is a "lifesaving measure in a substantial minority of patients who would otherwise die of cardiogenic shock."[1] Braunwald and Maroko[2] estimate that 20% of patients who would otherwise die can be saved, while another 20% can be stabilized for diagnosis and surgical intervention.

IABP "significantly reduced the magnitude and extent of acute myocardial ischemic injury"[3] in animal studies. The authors' preliminary clinical results also demonstrated reduced ischemia as well as hemodynamic improvement.

Time a critical factor

Hemodynamic criteria to determine if a patient who seems to be going into cardiogenic shock is responding to treatment have been developed by Leinbach.[4] These criteria are a major contribution to the effective application of IABP treatment since *early use* of the system greatly increases the chances of success. Buckley and associates[5] used the IABP in 27 heart-surgery patients who went into shock upon termination of cardiopulmonary bypass. Eighteen survived; 13 are long term survivors. Best results occurred with initiation of IABP therapy early in the postoperative period.

*Developed by Avco Corporation and manufactured for Roche Medical Electronics Division.

The IABP versus drugs

Dunkman and others[6] have concluded that "catecholamines may actually increase ventricular dysfunction and necrosis" whereas the IABP's enhancement of coronary perfusion and reduction of oxygen-consuming work in the left ventricle can save patients if applied before about 40% of the left ventricle is irretrievably damaged. Moreover, IABP permits safe use of drugs if needed.

AVCO, the most experienced system

The internal counterpulsation system most widely used clinically is the Avco IABP. There are some very practical reasons for this dominance.

Patented 3-chamber balloon design prevents end occlusion.

QRS triggered synchronization with normal and abnormal rhythms.

Automatic reset for changes in interval or loss of R wave.

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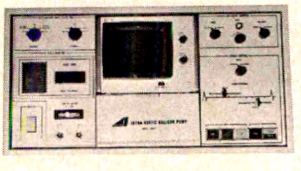

1. Editorial. JAMA 224:245. 1973.
2. Braunwald, E. and Maroko, P.R., Ann. Int. Med. 76:659, 1972.
3. Maroko, P.R. et al. Circulation 45:1150, 1972.
4. Leinbach, R.C., quoted in Emerg. Med. 5:107, 1973.
5. Buckley, M.J. et al (abstract). Circulation 46. Suppl. 2:76, 1972.
6. Dunkman, W.B. et al, Circulation 46:465. 1972.

ROCHE

Write for information on clinical experience and the annual Avco Pump Users' Meeting. Your local representative can arrange an Avco IABP demonstration in either a clinical or experimental setting.

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A72

Nitro-Bid® (nitroglycerin) therapy assists in the "total management" of your patient.

Nitro-Bid capsules reduce sublingual nitroglycerin requirements as they reduce the number of angina attacks . . . increase exercise tolerance.

Sustained-release Nitro-Bid Plateau CAPS® provide a metered sequence of medication during the night to protect against nocturnal angina attack.

The Third Step in Angina.*

After the classic "2-Step" Test aids in a diagnosis of angina, sustained-release Nitro-Bid® (nitroglycerin) is a logical third step. Here's why.

In angina secondary to arteriosclerotic heart disease, sustained-release

In titrating dosage, availability of different strengths "...is quite an asset..."[1]

Nitro-Bid 2.5 and Nitro-Bid 6.5 capsules afford two dosage strengths for convenience in increasing or decreasing dose to accommodate patient symptoms.

NITRO-BID® 2.5
(nitroglycerin 2.5 mg) Plateau CAPS®

NITRO-BID® 6.5
(nitroglycerin 6.5 mg) Plateau CAPS®

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

*"Possibly" effective:
For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12 hour intervals.
Reference: 1. Master, AM: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

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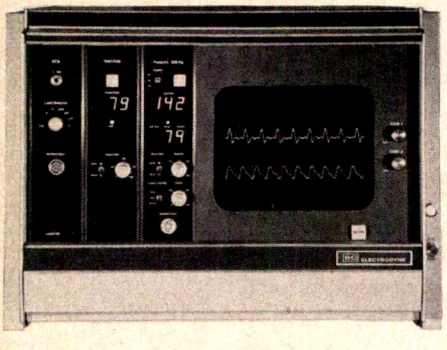

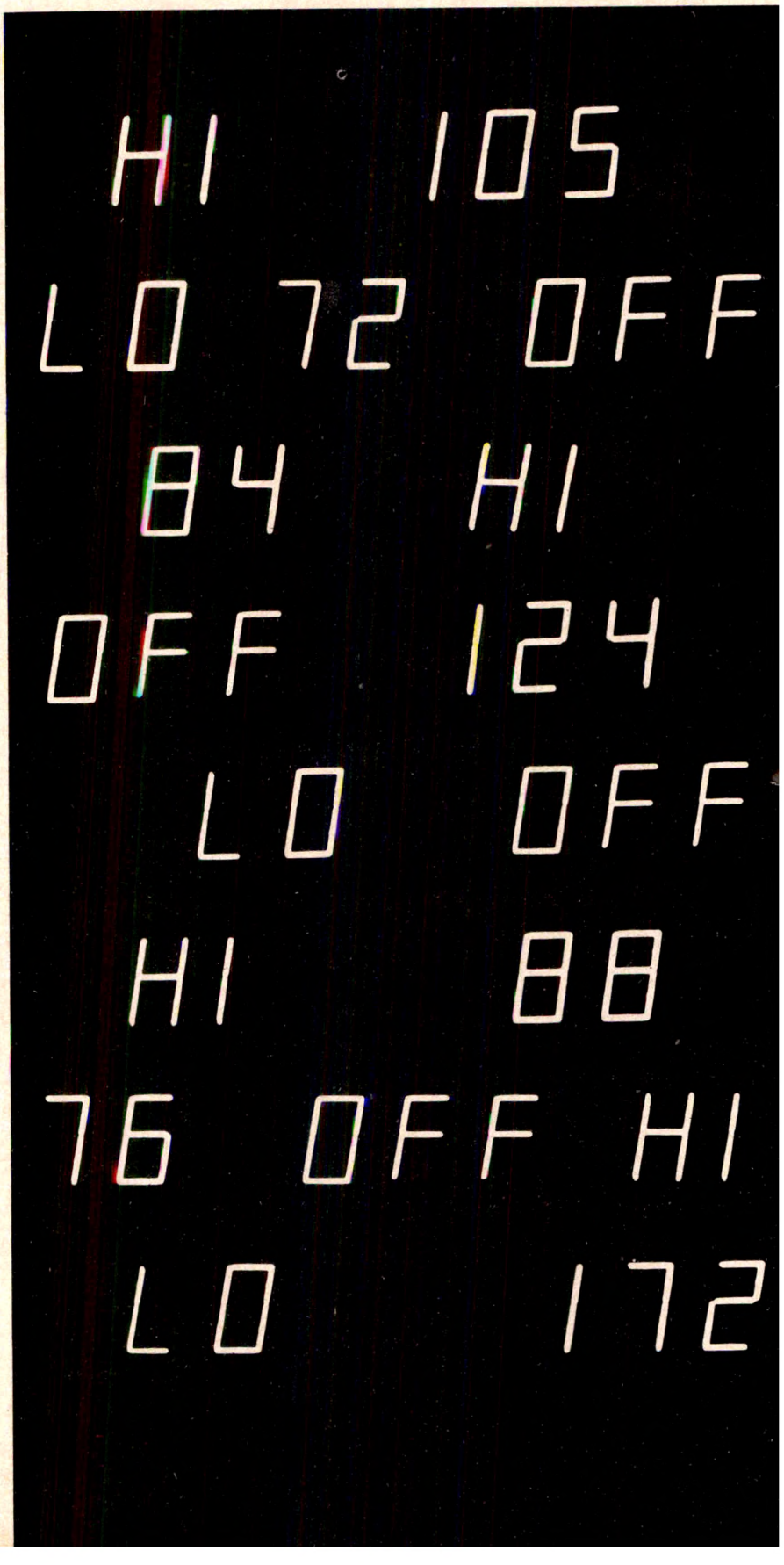

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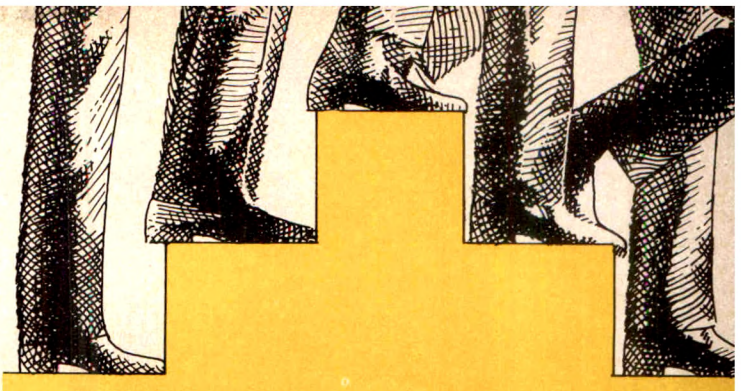

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Comparing electrocardiographic responses to standard exercise following placebo or sustained-release nitroglycerin (NITRO-BID® [nitroglycerin] capsules), "...6.5 mg doses produced a favorable response. Such findings indicate that large doses of nitrate escape degradation in the liver."[1]

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* **Indications**
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
Possibly effective:
For the management, prophylaxis or treatment of anginal attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy, hypotension.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12-hour intervals.

References:
1. Russek HI: What constitutes adequate medical therapy for the patient with angina pectoris? *Geriatrics* **29:**109-118, 1974.
2. Wendkos MH, Meshulam N: Comparative effects of placebo and sustained-release nitroglycerin in anginal subjects. *J Clin Pharmacol* **13:** 160-166, 1973.

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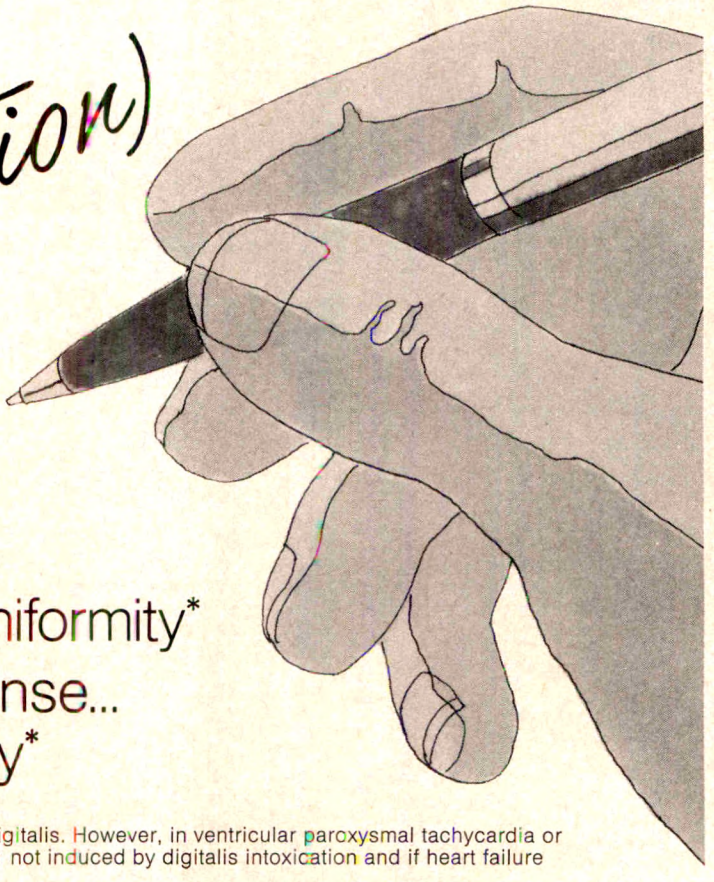

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precision quality control...
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Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

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- well tolerated to enhance patient cooperation – few G.I. disturbances

Contraindications: Quinaglute Dura-Tabs are contraindicated in patients with partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening; in patients manifesting idiosyncrasy or sensitivity to quinidine (e.g. febrile reactions, skin eruptions, thrombocytopenia, etc.), in patients with renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. It may be contraindicated in certain patients who have marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

Before prescribing or administering, please refer to QUINAGLUTE full product information.

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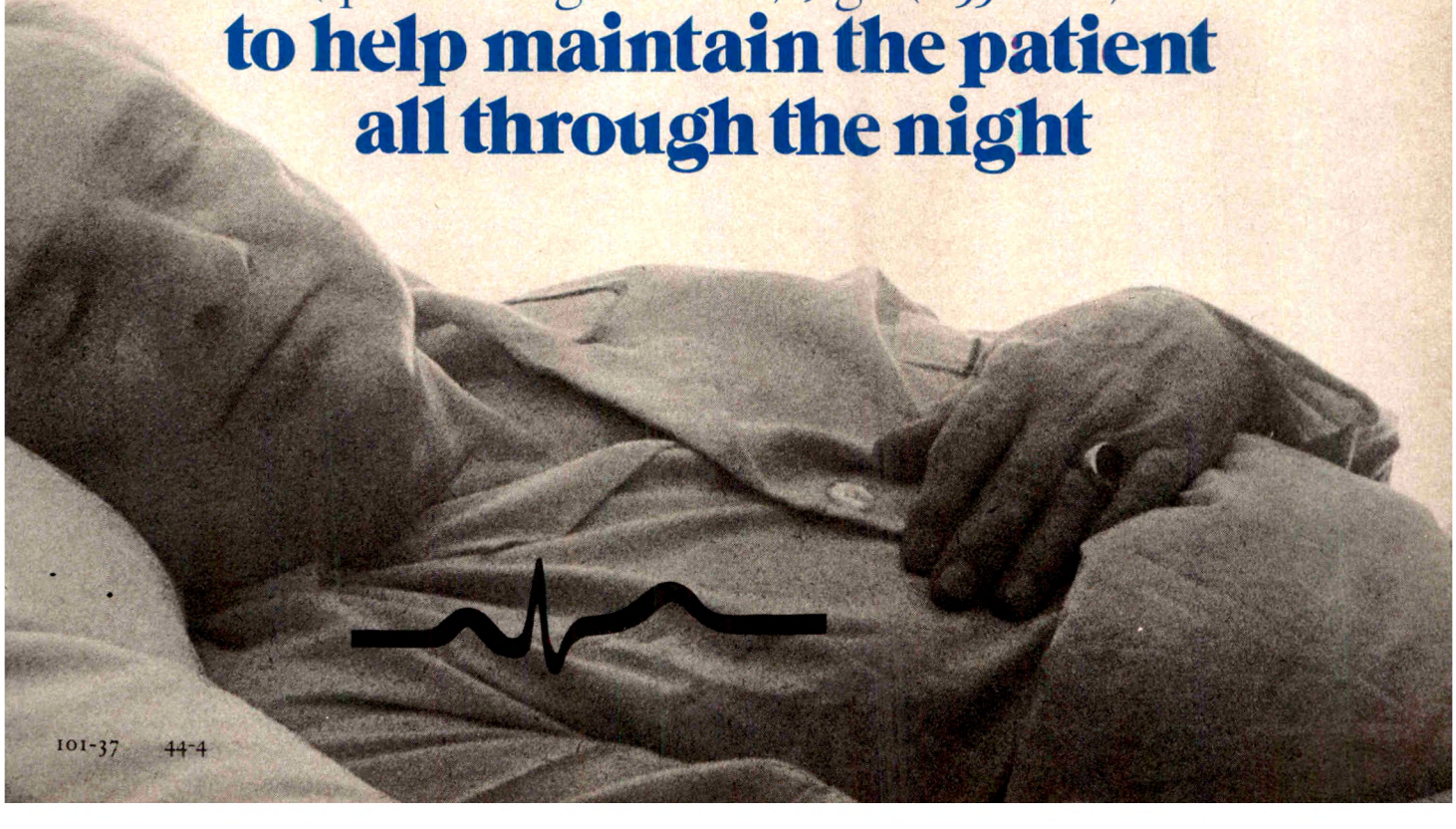
(quinidine gluconate) 5 gr. (0.33 Gm.)

to help maintain the patient all through the night



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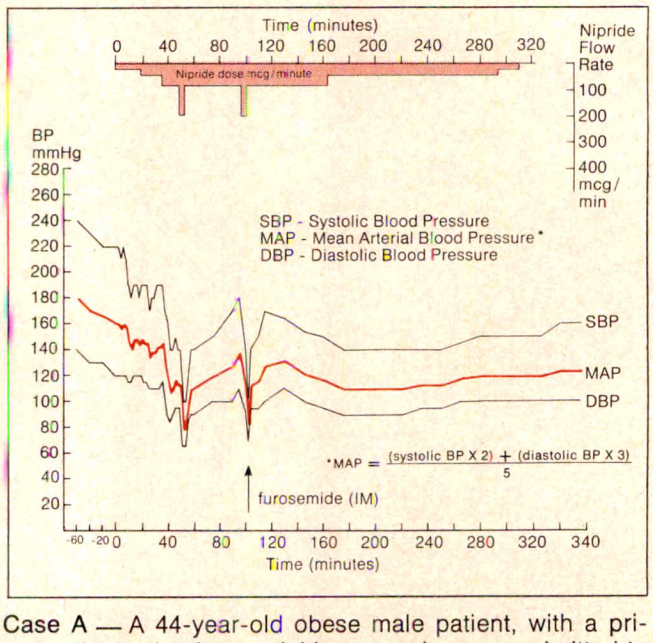
WORKS IMMEDIATELY. Nipride's antihypertensive effect may be seen within seconds after the beginning of intravenous infusion.

SHORT-ACTING. On cessation of Nipride administration, blood pressure will begin to rise within seconds to reach pretreatment levels in one to ten minutes. Thus, with careful monitoring and titration of Nipride dosage, the physician may reduce the patient's blood pressure as rapidly as he deems advisable, stabilize it at the desired level, sustain that level for hours — a few days if necessary — or until slower-acting medications become effective. Administration of oral antihypertensive medication should be started early in the course of treatment and Nipride dosage reduced accordingly as blood pressure begins stabilizing at desired levels. With frequent monitoring, hypotensive episodes may be avoided since Nipride permits minute-to-minute control of the patient's blood pressure.

Side Effects — reported side effects, such as nausea, retching, diaphoresis, etc., are probably related to excessively rapid lowering of blood pressure. *Contraindications* — compensatory hypertension, *e.g.,* arteriovenous shunt or coarctation of the aorta. *Compatibilities* — oral antihypertensive medications may be administered simultaneously with frequent monitoring to observe their additive effects. *Response* — consistent hypotensive effect regardless of patients' resistance to other antihypertensive medications. Reports of tachyphylaxis have been rare.

DOSAGE MUST BE INDIVIDUALIZED. Patient response varies widely over a range of 0.5 mcg/kg/min to 8.0 mcg/kg/min. It is evident, therefore, that infusion rates should be started at a minimal level, patient response observed for a few minutes, then dosage increased by a measured

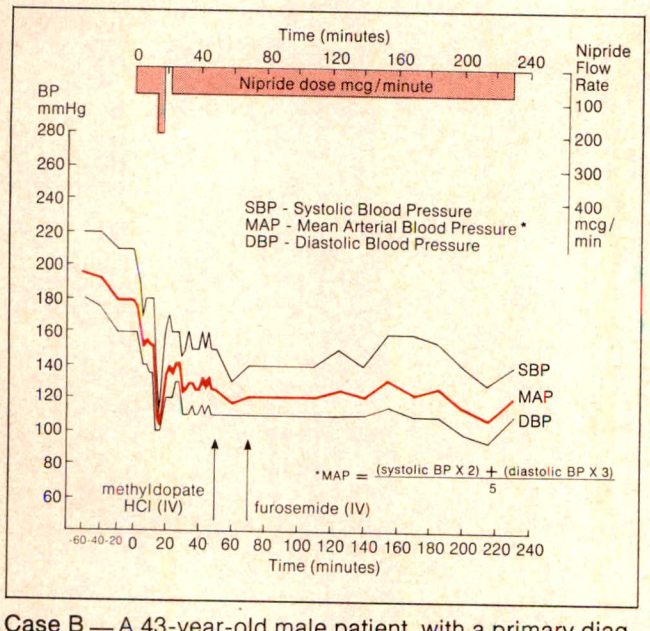


Case A — A 44-year-old obese male patient, with a primary diagnosis of essential hypertension, was admitted to a hospital with impending hypertensive encephalopathy. An infusion of Nipride (sodium nitroprusside) was started at approximately 25 mcg/min and then slowly increased to a dosage of 80 mcg/min during the first 40 minutes of administration. Dosage increase to 200 mcg/min at 50 minutes and 100 minutes resulted in sharp drops in blood pressure. As soon as the infusion was reduced to 80 mcg/min, there was an immediate rise in pressure to approximate levels previously observed with the same dosage. During Nipride administration, a single 40 mg IM dose of furosemide was given at approximately 100 minutes. The patient was subsequently maintained on oral medication (furosemide 40 mg, q.i.d., and triamterene 100 mg, q.i.d.).

ROCHE

for IV infusion.
in hypertensive crises.

increment and the process continued until blood pressure has reached a desired level. As examples of the procedure, Case A responded slowly, requiring increasing dosage increments; Case B responded rapidly, calling for a brief discontinuation of the infusion.

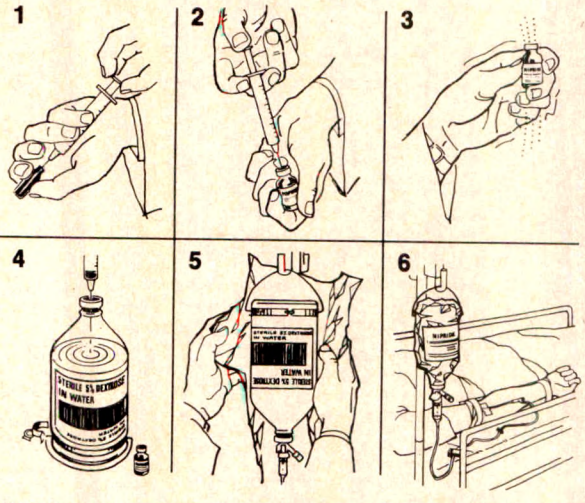


Case B — A 43-year-old male patient, with a primary diagnosis of essential hypertension and secondary diagnoses of impending left ventricular failure, headache and renal failure, was admitted to a hospital in hypertensive crisis. Nipride (sodium nitroprusside) infusion was started at 100 mcg/min, which produced a relatively small decrease in pressure. Infusion rate was then doubled, resulting in a sharp drop in blood pressure. Infusion was stopped for ten minutes until blood pressure rose, then resumed at the 100 mcg/min rate, which maintained pressure at a satisfactory level. Preliminary to discontinuation of Nipride, methyldopate HCl (500 mg IV) and furosemide (80 mg IV) were administered in single intravenous doses at 50 and 70 minutes respectively. The patient was subsequently maintained on oral medication (methyldopa 500 mg, q.i.d., and furosemide 40 mg, q.i.d.).

NIPRIDE MIXING PROCEDURE

FOR INTRAVENOUS INFUSION USE ONLY.
DO NOT ADMINISTER BY DIRECT INJECTION.

Nipride must be prepared immediately before administration. Once prepared, solutions containing Nipride should not be kept or used longer than four hours. No other medication should be added to the solution.



1. Withdraw 2 to 3 ml of sterile dextrose in water only. Any commercially available sterile dextrose in water in ampul form may be used. **2.** Aseptically add the dextrose in water to the 50-mg Nipride vial. **3.** Gently agitate to completely dissolve powder. **4.** Add all of the reconstituted solution to 500 or 1000 ml of sterile 5 percent dextrose in water depending on desired concentration. **5.** Promptly wrap Nipride solution in aluminum foil or other opaque material to protect from light. **6.** Administer prepared solution by infusion pump, micro-drip regulator or any similar device that will allow precise measurement of flow rate.

NIPRIDE™
(sodium nitroprusside)

50-mg vial

EMERGENCY BLOOD PRESSURE CONTROL

ROCHE

Please see following page for complete product information.

IN HYPERTENSIVE CRISES

EMERGENCY BLOOD PRESSURE CONTROL

NIPRIDE™
(sodium nitroprusside)

Nipride is only to be used as an infusion with sterile 5% dextrose in water. Not for direct injection.

DESCRIPTION: Nipride (sodium nitroprusside) in injectable form contains the equivalent of 50 mg of sodium nitroprusside dihydrate (sodium nitrosylpentacyanoferrate [III]) in a 5-ml amber-colored, rubber-stoppered vial. Chemically, sodium nitroprusside is $Na_2Fe(CN)_5NO{\cdot}2H_2O$. Nipride is a reddish-brown powder which is soluble in water. In aqueous solution, it is photosensitive and should be protected from light.

ACTIONS: Nipride is a potent, rapid acting, intravenous antihypertensive agent. This action is probably due to the nitroso (NO) group. Its effect is almost immediate and ends when the IV infusion is stopped. The brief duration of the drug's action is due to its rapid conversion to thiocyanate. The hypotensive effect is augmented by ganglionic blocking agents.

The hypotensive effects of Nipride are caused by peripheral vasodilatation as a result of a direct action on the blood vessels, independent of autonomic innervation. No relaxation is seen in the smooth muscle of the uterus or duodenum *in situ* in animals.

INDICATIONS: Nipride is indicated for the immediate reduction of blood pressure of patients in hypertensive crises. Concomitant oral antihypertensive medication should be started while the hypertensive emergency is being brought under control with Nipride. There is no contraindication in using Nipride simultaneously with oral antihypertensive medications.

CONTRAINDICATIONS: Nipride should not be used in the treatment of compensatory hypertension, *e.g.,* arteriovenous shunt or coarctation of the aorta.

WARNINGS: Nipride is only to be used as an infusion with sterile 5% dextrose in water. Not for direct injection.

Since an end product of Nipride metabolism, thiocyanate, inhibits both the uptake and binding of iodine, caution should be exercised in using Nipride in patients with hypothyroidism or severe renal impairment.

Blood levels of thiocyanate should be determined if treatment is to be extended in patients with severe renal dysfunction. Although intravenous infusions of Nipride are not intended for long-term use, as long as blood thiocyanate levels are measured daily and do not exceed 10 mg/100 ml, it is probably safe to continue with the infusion until the patient can be safely treated with oral antihypertensive medications.

Hypertensive patients are more sensitive to the intravenous effect of sodium nitroprusside than are normotensive subjects. Patients who are receiving concomitant antihypertensive medications are more sensitive to the hypotensive effect of sodium nitroprusside and the dosage of Nipride should be adjusted accordingly.

Usage in Pregnancy: The safety of Nipride in women who are or who may become pregnant has not been established; hence, it should be given only when the potential benefits have been weighed against possible hazard to mother and child.

Usage in Children: The safety of Nipride in children has not been established. Clinical experience is limited. Further studies are in progress to determine its proper dosage and administration.

PRECAUTIONS: Adequate facilities, equipment and personnel should be available for frequent and vigilant monitoring of blood pressure, since the hypotensive effect of Nipride (sodium nitroprusside) occurs rapidly. When the infusion is slowed or stopped, blood pressure usually begins to rise immediately and returns to pretreatment levels within one to ten minutes. It should be used with caution and initially in low doses in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

Because of the rapid onset of action and potency of Nipride, it should preferably be administered with the use of an infusion pump, micro-drip regulator or any similar device that would allow precise measurement of the flow rate.

Once dissolved in solution, Nipride tends to deteriorate in the presence of light. Therefore, it should be protected from light by wrapping the container of the prepared solution with aluminum foil or other opaque materials. Solutions of Nipride should not be kept or used longer than four hours.

Nipride in aqueous solution yields the nitroprusside ion which reacts with even minute quantities of a wide variety of inorganic and organic substances to form usually highly colored reaction products (blue, green or dark red). If this occurs the infusion should be replaced.

ADVERSE REACTIONS: Nausea, retching, diaphoresis, apprehension, headache, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain have been noted with too rapid reduction in blood pressure, but these symptoms rapidly disappeared with slowing of the rate of the infusion or temporary discontinuation of infusion and did not reappear with continued slower rate of administration.

One case of hypothyroidism following prolonged therapy with intravenous sodium nitroprusside has been reported. A patient with severe hypertension with uremia received 3900 mg of sodium nitroprusside intravenously over a period of 21 days. This is one of the longest reported intravenous uses of this agent. There was no tachyphylaxis, but the patient developed evidence of hypothyroidism, together with retention of thiocyanate (9.5 mg/100 ml). With peritoneal dialysis the thiocyanate level diminished and the signs of hypothyroidism subsided.

DOSAGE AND ADMINISTRATION: The contents of a 50-mg Nipride vial should be dissolved in 2 to 3 ml of dextrose in water. No other diluent should be used. Depending on the desired concentration, all of the prepared stock solution should be diluted in 500 to 1000 ml of 5 percent dextrose in water and promptly wrapped in aluminum foil or other opaque materials to protect from light. Both the stock solution and the infusion solution should be freshly prepared and any unused portion discarded. The freshly prepared solution for infusion has a very faint brownish tint. If it is highly colored, it should be discarded (see PRECAUTIONS). *Once prepared, the solution should not be kept or used longer than four hours. The infusion fluid used for the administration of Nipride should not be employed as a vehicle for simultaneous administration of any other drug.*

In patients who are not receiving antihypertensive drugs, the average dose of Nipride is 3 μg/kg/minute (range of 0.5 to 8 μg/kg/minute). Usually, an average of 200 μg/minute (range of 20 to 400 μg/minute) is sufficient to maintain the blood pressure at 30 to 40 percent lower than the pretreatment diastolic blood pressure levels. In hypertensive patients receiving concomitant antihypertensive medications, smaller doses are required. In order to avoid excessive levels of thiocyanate and lessen the possibility of a precipitous drop in blood pressure, the maximum recommended dose is 800 μg/minute.

1 Vial (50 mg) Nipride (sodium nitroprusside) in 500 ml 5% DW (100 μg/ml)

Dose/kg	μg/kg/min	ml/kg/min
Average	3	0.03
Range	0.5 to 8	0.005 to 0.08
Dose for a 70 kg patient	**μg/70 kg/min**	**ml/70 kg/min**
Average	200	2.0
Range	35 to 560	0.35 to 5.6

The intravenous infusion of Nipride should be administered by an infusion pump, microdrip regulator or any similar device that will allow precise measurement of the flow rate. Care should be taken to avoid extravasation. The rate of administration should be adjusted to maintain the desired antihypertensive effect, as determined by frequent blood pressure determinations. Nipride infusion may be continued until the patient can safely be treated with oral antihypertensive medications alone.

HOW SUPPLIED: Nipride injectable is supplied in 5-ml amber-colored vials containing the equivalent of 50 mg sodium nitroprusside dihydrate for reconstitution with dextrose in water (available singly and in packages of 10).

HUMAN PHARMACOLOGY: Sodium nitroprusside administered intravenously to hypertensive and normotensive patients produced a marked lowering of the arterial blood pressure, slight increase in heart rate, a mild decrease in cardiac output and a moderate diminution in calculated total peripheral vascular resistance.

The decrease in calculated total peripheral vascular resistance suggests arteriolar vasodilatation. The decreases in cardiac and stroke index noted may be due to the peripheral vascular pooling of blood.

In hypertensive patients, moderate depressor doses induce renal vasodilatation roughly equivalent to the decrease in pressure without an appreciable increase in renal blood flow or a decrease in glomerular filtration.

In normotensive subjects, acute reduction of mean arterial pressure to 60 to 75 mm Hg by infusion of sodium nitroprusside caused significant increase in renin activity of renal venous plasma in correlation with a degree of reduction in pressure. Renal response to reduction in pressure was more striking in renovascular hypertensive patients, with significant increase in renin release occurring from the involved kidney at mean arterial pressures ranging from 90 to 137 mm Hg. Furthermore, the magnitude of renin release from the involved kidney was significantly greater when compared with that in normotensive subjects, while in the contralateral, uninvolved kidney, no significant release of renin was detected during the reduction of pressure.

THIS PRODUCT INFORMATION ISSUED JULY 1974

For a copy of the comprehensive Nipride Monograph, please write to Professional Services Department, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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FLOW PROBES

for clinical applications

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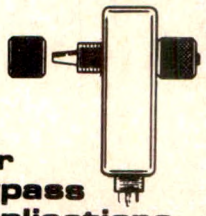
- For rapid analysis of flow through exposed blood vessels
- Use with Biotronex clinical blood flowmeter

FLOW PROBES



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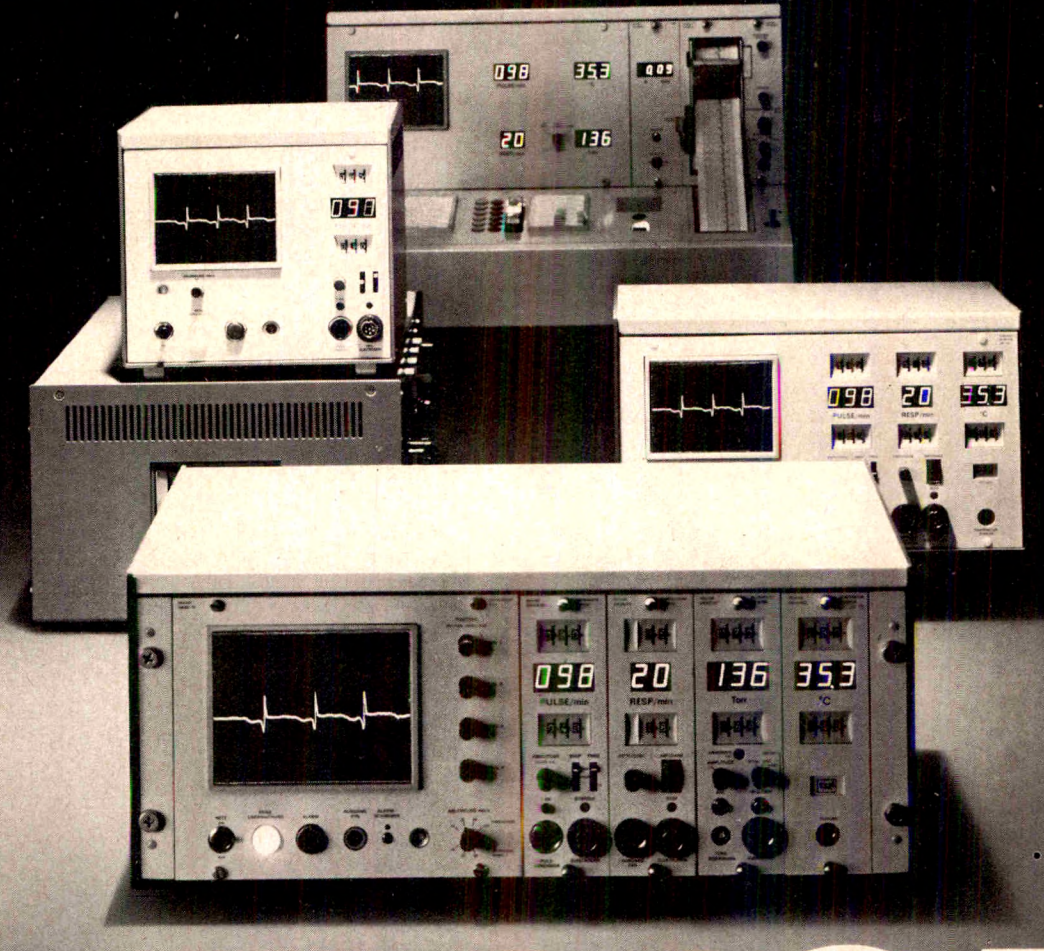

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Two new modules give the Smith Kline Instruments Ekoline 20A® an unmatched multi-trace capability. The Isolated Sweep/EKG Module and the Multi-Parameter Amplifier Module enable the E20A Ultrasonoscope to produce traces for ultrasound, EKG, phono and carotid pulse or apex. Combine this with the Fiber-optic Recorder and the result is high quality, grey scale strip chart recordings of pertinent information—at a surprisingly low cost.

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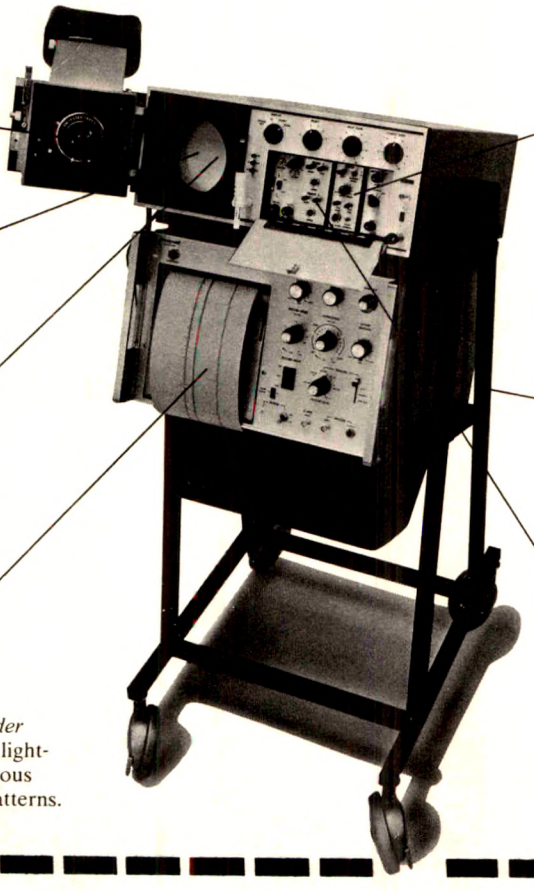

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REQUEST FOR ADDITIONAL INFORMATION

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☐ Have representative call me to arrange a demonstration.

☐ Send detailed literature.

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3. Permits substantial reduction of furosemide or thiazide dosage while preserving diuretic effect.

Before prescribing see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy.

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Dyrenium (triamterene, SK&F) and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When Dyrenium is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.
Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 100 mg. capsules in bottles of 100; in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co., Carolina, P.R. 00630
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MARCH 1975

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Myocardial Imaging in Regional Ischemia and Infarction

Correlation of Heart Sounds and Echocardiogram

Contents on Page A9

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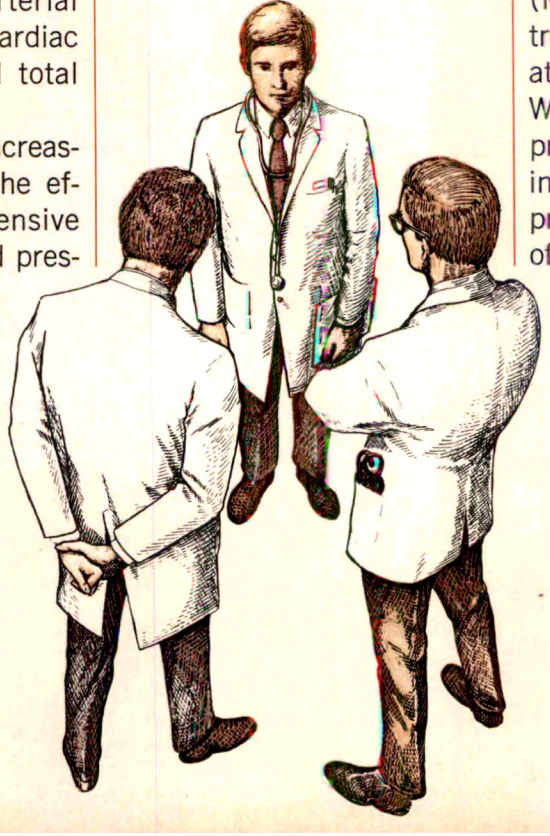
A YORKE MEDICAL JOURNAL

The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?

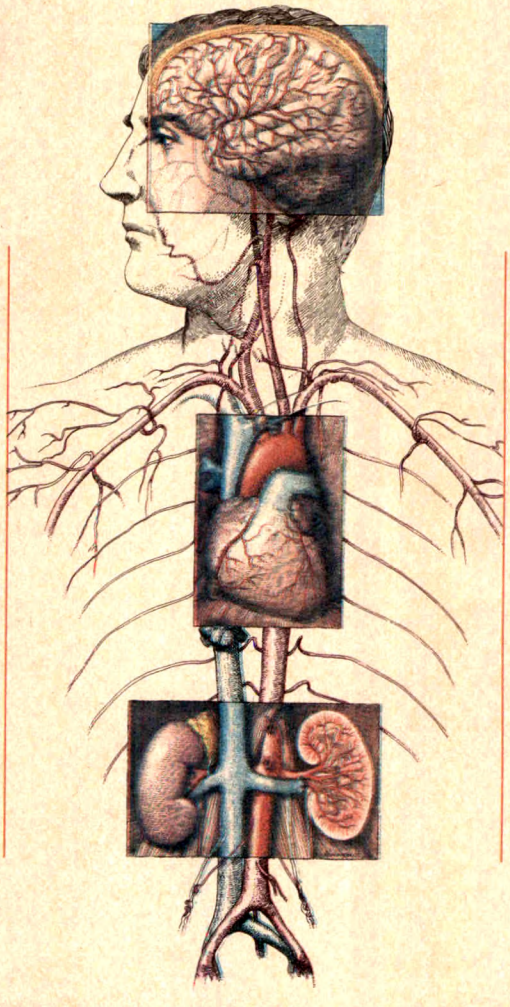


With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in

the more physicians rely on this unique antihypertensive

lowering blood pressure. But there are other considerations as well. Cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is actually slowed. Peripheral resistance is apparently reduced. ALDOMET does not usually compromise existing renal function; it generally does not reduce renal blood flow, glomerular filtration rate, or filtration fraction. And ALDOMET usually does not cause symptomatic postural or exercise hypotension.



Contraindications include active hepatic disease and known sensitivity to the drug. Use with caution in patients with a history of liver disease or dysfunction. Not recommended in pheochromocytoma or pregnancy.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

In most cases of sustained moderate hypertension

TABLETS, 250 mg and 500 mg

ALDOMET®

(METHYLDOPA | MSD)

smoothly lowers blood pressure

NEW now available in 500 mg TABLETS as well as the standard 250-mg tablets

For a brief summary of prescribing information, please see following page.

In most cases of sustained moderate hypertension

ALDOMET®
(METHYLDOPA | MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis. Known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between six and twelve months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at six and twelve months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first six to twelve weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur.

Use in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Methyldopa may interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has occurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure are occasionally seen and include dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency. Angina pectoris may be aggravated. Symptoms of orthostatic hypotension may occur; if symptoms occur, reduction of dosage is suggested. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distention, constipation, flatus, and diarrhea occur occasionally; these generally can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently and are relieved by administering a thiazide diuretic; if edema progresses or signs of pulmonary congestion appear, discontinue drug. A rise in BUN has been observed. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, Bell's palsy, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Note: Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Maximal recommended daily dose is 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

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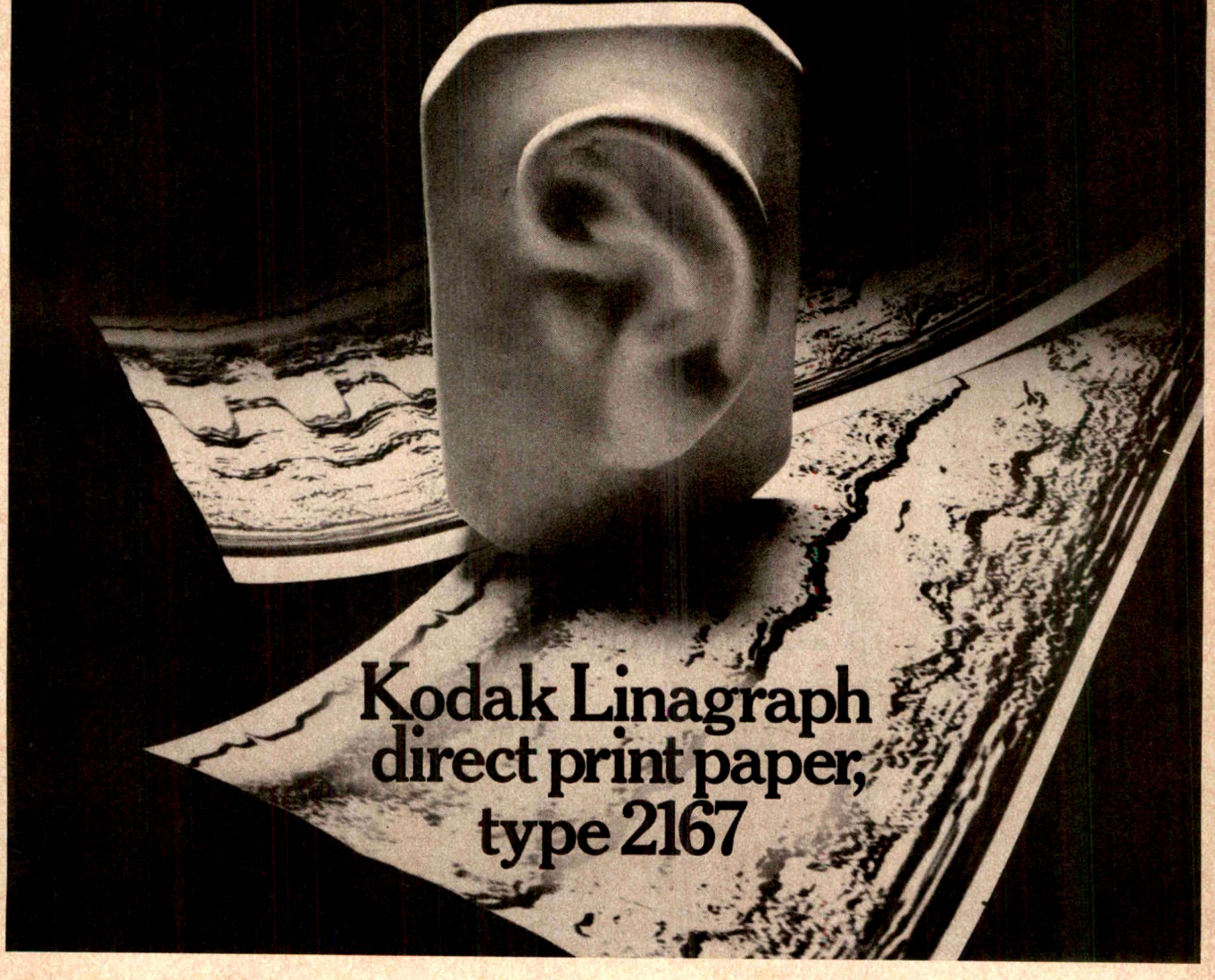

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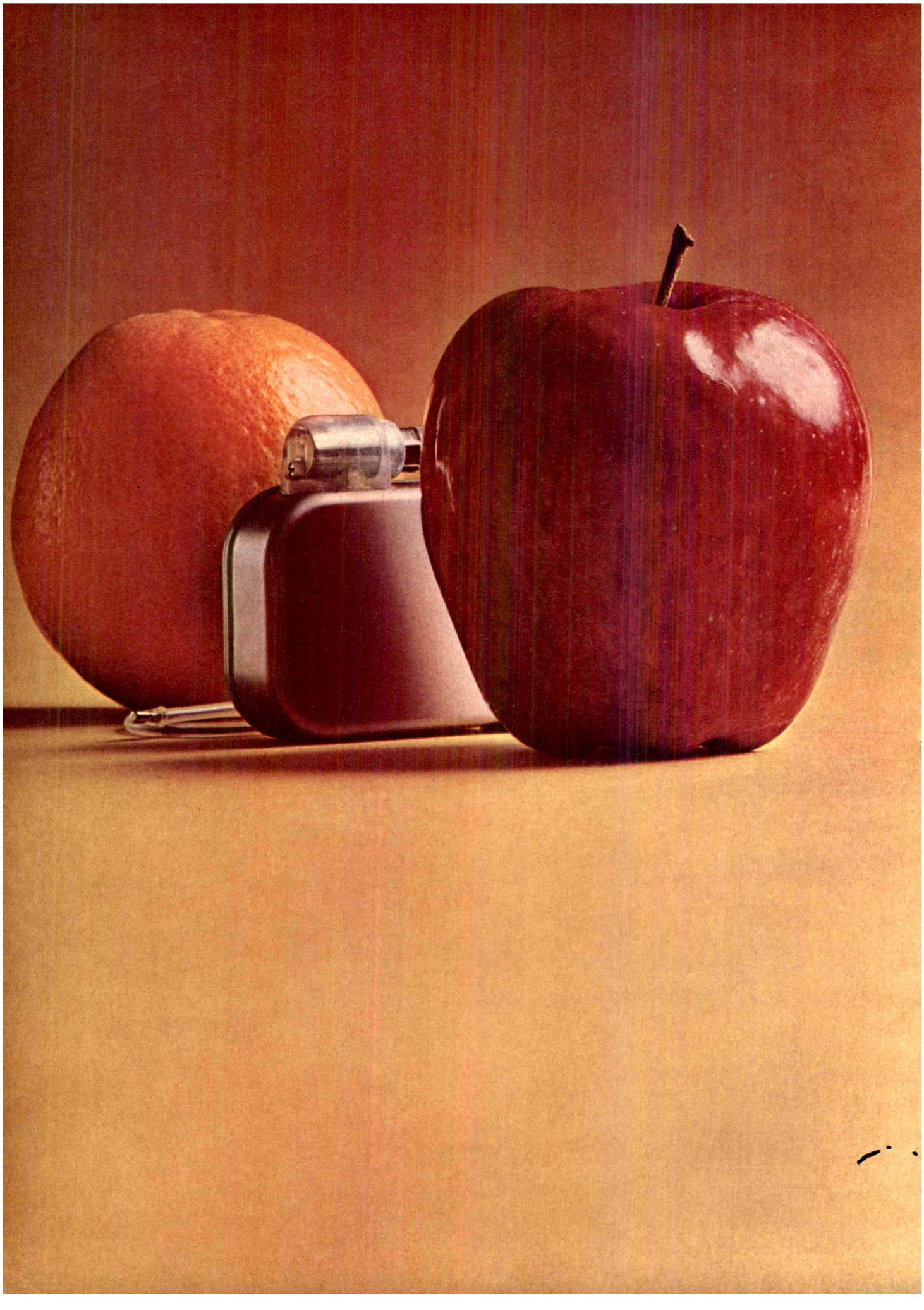

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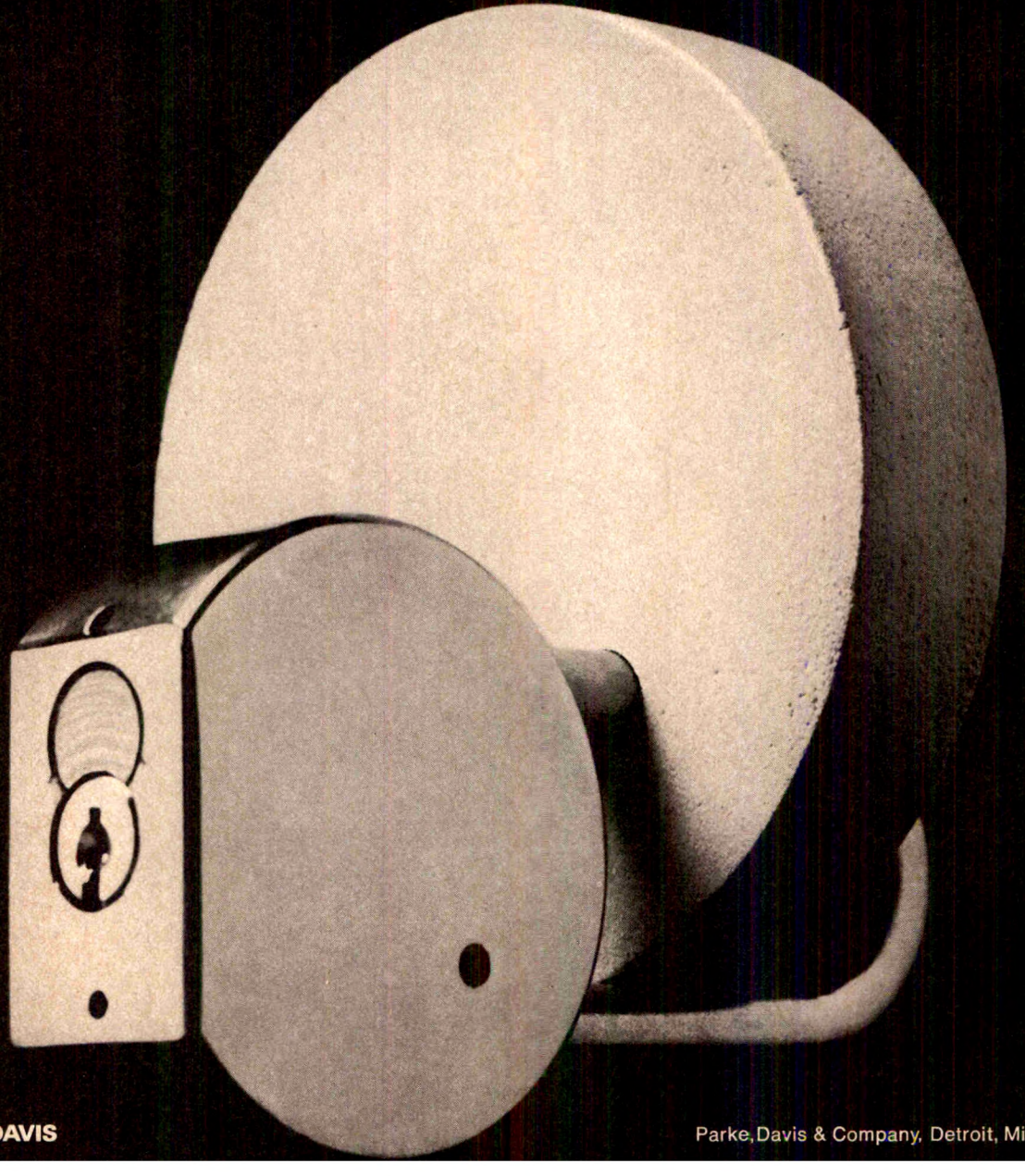

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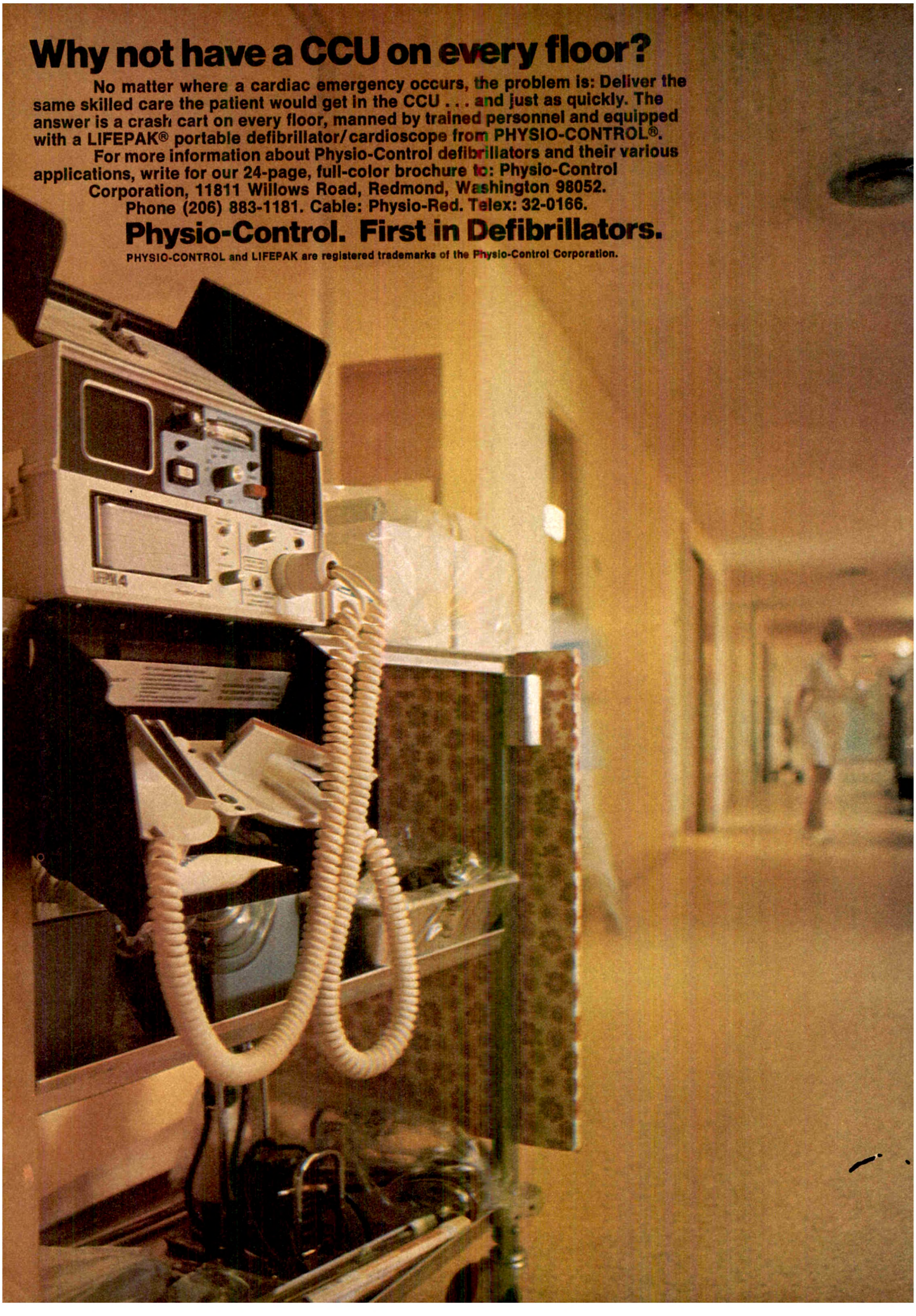

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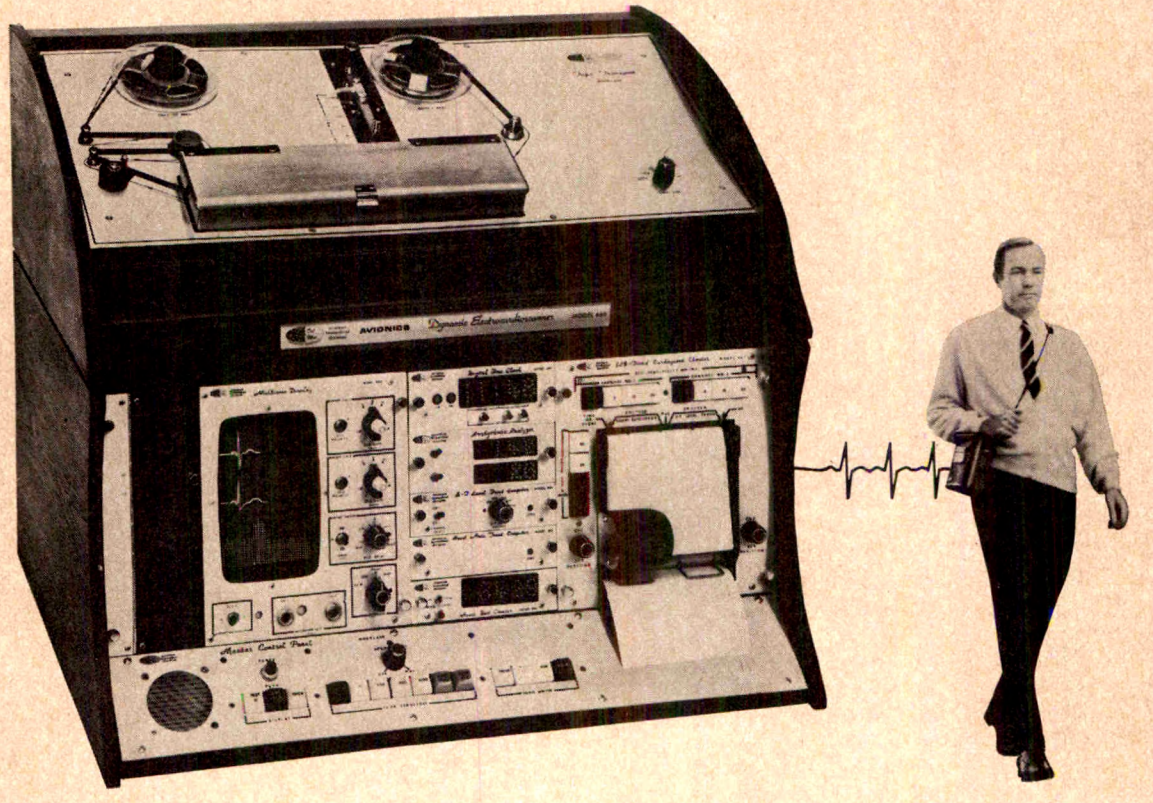

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WALTER L. HENRY, CHESTER E. CLARK, JAMES M. GRIFFITH and STEPHEN E. EPSTEIN

One- and two-dimensional echocardiographic studies of 100 patients with obstructive asymmetric septal hypertrophy suggest narrowing of the left ventricular outflow tract at the onset of systole by forward movement of the mitral valve and the hydrodynamic forces generated by contraction of the left ventricle produce the left ventricular outflow obstruction. Contraction of the malaligned papillary muscles did not cause the abnormal forward mitral valve motion.

346 **First Heart Sound and Ejection Sounds. Echocardiographic and Phonocardiographic Correlation with Valvular Events**

WINFRIED WAIDER and ERNEST CRAIGE

These studies in 49 subjects with audible splitting of the first heart sound or an ejection sound show a precise relation between complete closure of the atrioventricular (A-V) valves in the echocardiogram and the high-frequency components of S_1 in the phonocardiogram. The observations support the postulate that M_1, T_1 and the ejection sounds occur in association with closing or opening of the valves with consequent sudden deceleration or acceleration of a column of blood that causes vibrations of the cardiohemic system and audible sounds.

357 **Pericardial Rub. Prospective, Multiple Observer Investigation of Pericardial Friction in 100 Patients**

DAVID H. SPODICK

This study of 100 patients with pericardial friction detected triphasic pericardial rubs in 56 percent of patients with sinus rhythm. Summation of the ventricular diastolic rub with the atrial systolic rub concealed an additional 10 percent of potential triphasic friction. Sixty-one patients actually had a triphasic rub. Extension of the neck, said to increase the intensity of pericardial rubs, proved an unreliable and confusing maneuver, having no dependable effect on rub intensity.

Continued on page A13

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363 Prolapse of the Posterior Leaflet of the Mitral Valve Associated with Secundum Atrial Septal Defect

AMADEO BETRIU, E. DOUGLAS WIGLE, CLARENCE H. FELDERHOF and MICHAEL J. McLOUGHLIN

In this study of 54 patients with secundum atrial septal defect, left ventricular cineangiograms showed prolapse of the posterior leaflet of the mitral valve in 37 percent (20 patients); 20 percent (11 patients) had a pansystolic murmur or a mid-systolic click, or both; but 17 percent (9 patients) had no clinical evidence of such prolapse. This complication should be suspected in patients with secundum atrial septal defect complaining of chest pain or presyncopal or syncopal attacks. In the future, echocardiography may help detect mitral prolapse not detected by auscultation.

EXPERIMENTAL STUDIES

370 Effect of Digoxin on Sinus Nodal Reentry in the Dog

KARLEN L. PAULAY and ANTHONY N. DAMATO

Sinus nodal reentry was relatively unaffected by the infusions of digoxin in 18 of 20 open chest mongrel dogs. Digitalis toxicity, manifested as increased atrial and ventricular automaticity in 14 and as advanced A-V block in 4, developed before reentry was abolished. This relative insensitivity of sinus nodal reentry to digitalis contrasts with its sensitivity to quinidine.

376 Effects of Aminophylline on the Threshold for Initiating Ventricular Fibrillation During Respiratory Failure

LEONARD N. HOROWITZ, JOSEPH F. SPEAR, E. NEIL MOORE and ROBERT ROGERS

In anesthetized open chest dog experiments aminophylline exerted a biphasic effect on the ventricular myocardium; during infusion it predisposed the ventricular myocardium to the initiation of fibrillation and after infusion it protected the myocardium by reducing the ease by which fibrillation could be initiated. Respiratory failure potentiates such aminophylline-induced vulnerability to ventricular fibrillation. Such effects in man remain inferential.

METHODS

380 Myocardial Imaging with Indium-113m- and Technetium-99m-Macroaggregated Albumin. New Procedure for Identification of Stress-Induced Regional Ischemia

JAMES L. RITCHIE, GLEN W. HAMILTON, K. LANCE GOULD, DAVID ALLEN, J. WARD KENNEDY and KARL E. HAMMERMEISTER

This study documents the feasibility of using dual isotope intracoronary macroaggregated radioactive albumin imaging to detect impaired regional blood flow distribution during periods of increased coronary blood flow stimulated by the intracoronary injection of Hypaque-M, 75 percent. In this series 30 of 40 patients with arteriographically proved coronary artery disease manifested new myocardial perfusion defects in the study performed during coronary hyperemia. This method may help ascertain the hemodynamic importance of a questionable stenosis in arteriograms and identify viable myocardium contiguous to infarcted myocardium.

Continued on page A15

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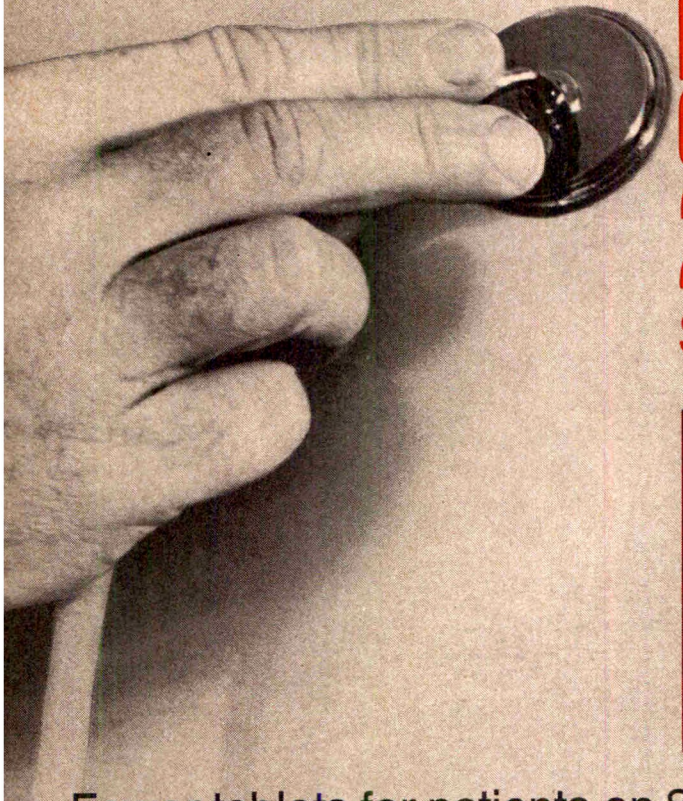

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390 Detection of Acute Myocardial Infarction by Technetium-99m Polyphosphate

PETER McLAUGHLIN, GEOFFREY COATES, DONALD WOOD, TREVOR CRADDUCK and JOHN MORCH

Technetium-99m polyphosphate myocardial imaging studies were positive in 16 tests performed 4 to 20 days after transmural myocardial infarction in 12 patients and were normal in 16 of 17 control tests. These results indicate this test appears to be a promising means of detecting and locating transmural myocardial infarction, and may be helpful after cardiac surgery when standard diagnostic aids are difficult to interpret.

PEDIATRIC CARDIOLOGY

397 Late Systolic Murmur of Rheumatic Mitral Insufficiency

LEONARD STEINFELD, IVAN DIMICH, HOWARD RAPPAPORT and MURRAY BARON

Thirty-four of 184 patients with acute rheumatic fever and associated mitral insufficiency manifested a mid-late systolic murmur or a nonejection click, or both, during a 15 year follow-up period. None had T wave abnormalities commonly seen in the familial variety of mitral valve prolapse syndrome. The murmur disappeared in four patients and their echocardiograms have failed to show mitral valve prolapse.

402 Tetralogy of Fallot: A Morphometric and Geometric Study

ANTON E. BECKER, MIKE CONNOR and ROBERT H. ANDERSON

Data from 14 examples of tetralogy of Fallot, indicating that conal rotation has occurred in addition to anterior deviation, support the hypothesis of "lack of conal inversion" and conal malseptation as the morphogenetic mechanisms in this congenital anomaly.

REPORTS ON THERAPY

413 Potassium Canrenoate in the Treatment of Long-Term Digoxin-Induced Arrhythmias in Conscious Dogs

NORBERTO T. deGUZMAN and BILLY K. YEH

Potassium canrenoate, a diuretic agent with positive inotropic effects, alleviated in dogs such digoxin-induced cardiac arrhythmias as sinus bradycardia, sinoatrial block and A-V conduction disturbances, and suppressed premature supraventricular and ventricular beats and ventricular tachycardias. A possible mechanism is the competitive displacement of digitalis from membrane sites by canrenoate, whose molecular structure resembles that of digitalis.

Continued on page A17

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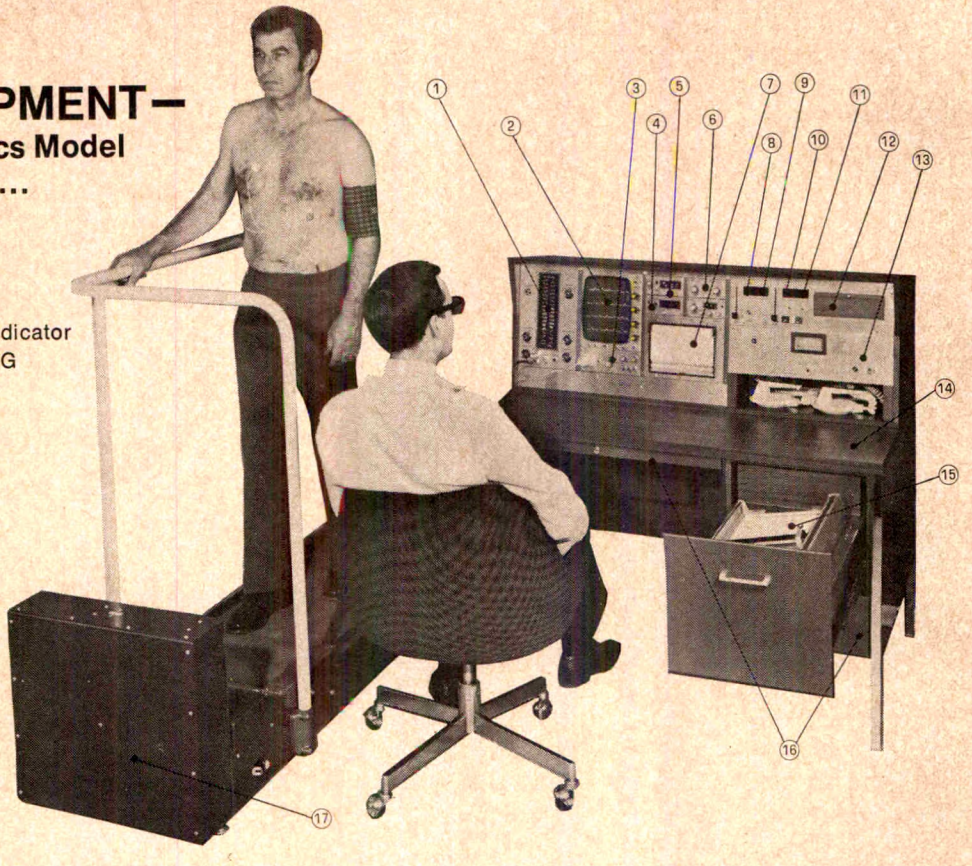

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CONTENTS

REVIEWS

421 Pathophysiology of Second Degree Atrioventricular Block: A Unified Hypothesis

NABIL EL-SHERIF, BENJAMIN J. SCHERLAG and RALPH LAZZARA

Evidence cited in this review suggests that Mobitz type II and the Wenckebach type of conduction represent different degrees of the same disorder rather than two distinct electrophysiologic processes. During acute ischemia, the His-Purkinje system resembles the A-V node in showing Wenckebach periodicity. Although the empirical classification of second degree A-V block into types I and II is still clinically useful, a new classification based on the actual electrophysiologic mechanism as described in this article appears more appropriate.

DIAGNOSTIC SHELF

435 Loud First Heart Sound with Long P-R Intervals

NAYAB ALI

An atrial echo (reciprocal) beat detected within the QRS complex only in the intracardiac electrocardiogram and not seen in the surface tracing caused an unusually loud first heart sound associated with the longest P-R interval in a 14 year old boy with partial A-V block of the Wenckebach type.

CASE REPORTS

439 Traumatic Right Coronary Arterial-Right Atrial Fistula

GORDON P. ANDERSON, ARNOLD ADICOFF, GEORGE J. MOTSAY, YOSHIO SAKO and FREDARICK L. GOBEL

As in this 25 year old airman who sustained multiple shrapnel wounds to the body resulting in a right coronary arterial-right atrial fistula 3 years later, fistula formation of this type may be a late complication of penetrating thoracic injuries. The fistula was successfully repaired, but the hypokinetic inferior wall remained unchanged after closure of the fistula.

444 Echocardiographic Findings in Right Coronary Arterial-Right Ventricular Fistula. Report of a Neonate with Fatal Congestive Heart Failure

MARIO S. VERANI and RONALD M. LAUER

Although coronary arteriovenous fistula rarely causes congestive heart failure in a neonate, this report describes a case in which the echocardiogram suggested an unusual location of a left to right shunt and cardiac catheterization and angiography established the diagnosis. The hemodynamic condition deteriorated quickly after angiography and the child died as a result of sudden respiratory hemorrhage and cardiac arrest.

448 Transmural Myocardial Infarction During Pregnancy

LEWIS SASSE, RICHARD WAGNER and FRANK E. MURRAY

Prolonged but reversible coronary spasm due to release of renin from the uterus appears the most likely cause of transmural myocardial infarction in two pregnant women. In both, coronary arteriograms were normal several months later.

Continued on page A19

Beat after beat...day after day

CARDIOQUIN tablets

(quinidine polygalacturonate)

To convert...to MAINTAIN normal sinus rhythm

After conversion of cardiac arrhythmias—whether with CARDIOQUIN Tablets or some other current method—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required in most cases to maintain normal sinus rhythm.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heartblock; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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SPECIAL DEPARTMENTS

453 Reviews in Cardiology

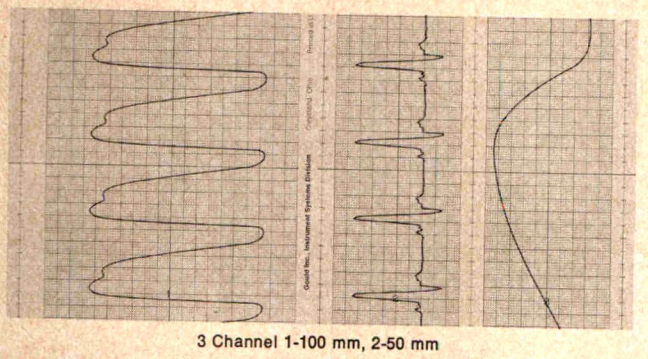
456 Book Reviews

457 American College of Cardiology News

Introducing the Gould 2400, the most significant advance in biophysical recorders in the past decade.

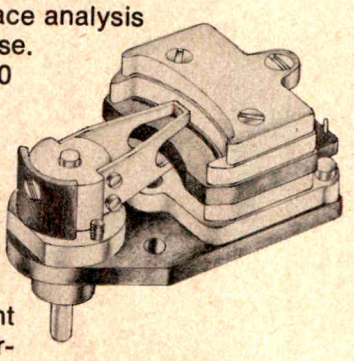
Gould direct writing recorders have been the standard of the industry since the early 1960's. Now we've advanced the state of the art even further. The brand-new Gould 2400 wide channel recorder is being called the best performing, most versatile, most reliable multi-channel biophysical recording system you can buy. Here's why.

The Gould 2400, with its full 100 mm wide channel, is ideal for research or critical diagnostic applications. The Gould 2400 has the best resolution of any wide channel recorder on the market. This high display resolution, along with the 100 mm wide chart presentation,



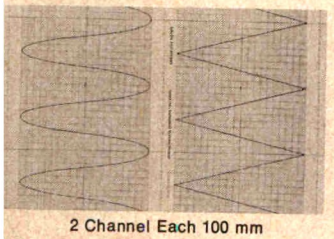
3 Channel 1-100 mm, 2-50 mm

makes your critical trace analysis easier and more precise.

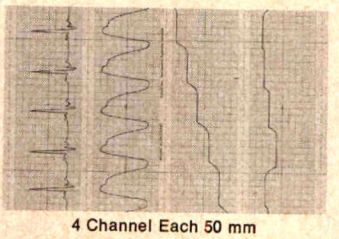


The heart of the 2400 is a 100 grams/mm high-stiffness servo controlled penmotor with an exceptional frequency response. The high precision non-contact Metrisite® servo feedback element enforces 99.65% linearity over the entire channel width.

The Gould 2400 can meet just about any biophysical application. The 2400 is available in two, three and four channel configurations utilizing combinations of 50 mm and 100 mm channels totaling 200 mm. Left and right margin



2 Channel Each 100 mm

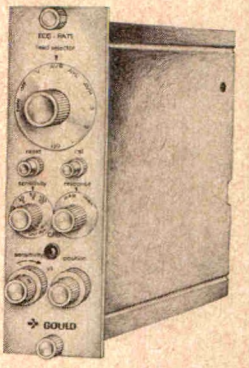


4 Channel Each 50 mm

event markers are standard and may be activated by remote switch closures TTL inputs, or by an internal programmable timer.

The Gould 2400 has a full range of biophysical signal conditioners. There isn't a direct writing recorder on the market today that can match the Gould 2400 for range of available biophysical signal conditioners.

Our couplers and preamplifiers have been designed for physicians and researchers. You can choose from any of 12 off-the-shelf units, ranging from the industry standard ECG to Gould's unique Blood Pressure Computer which gives 14 different outputs. Another standard unit is the Gould Temperature Preamplifier with an accuracy of 0.2% of a degree and a design that enables you to use it with 25 different probes without recalibration.



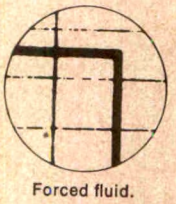
Whatever your special signal conditioning requirements, chances are we have a packaged solution for it.

The Gould 2400 has an unequalled frequency response. The 2400's frequency response is an outstanding 30 Hz at 100 mm, 50 Hz at 50 mm and up to 125 Hz at reduced amplitude.

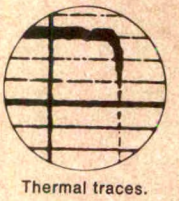
The Gould 2400 has 12 chart speeds. Twelve chart speeds from 0.05 to 200 mm/sec are pushbutton selected and activated by either front panel or remote controls. A front panel paper supply indicator operates like a fuel gauge and a pilot lamp lights up when a new roll is required assuring full usage of the entire paper supply.

The Gould 2400's modular design means ease of service. The Gould 2400's ink shutoff valves, adjustment pots, penmotors, drive motor and the transmission are all readily accessible. Disposable ink cartridges are easily replaced in seconds.

The Gould 2400 comes with many exclusives. The Gould pressurized inking system gives you the highest quality traces, with no smudges, smears, skips or puddles. Our Metrisite non-contact servo loop feedback device eliminates slide wires and guarantees a better than 99.65% linearity. Our recorders have a rectilinear presentation rather than a curvilinear one. And our high penmotor stiffness (100 grams/mm) provides an unexcelled rise time.



Forced fluid.



Thermal traces.

The Gould 2400: the ultimate performer for biophysical recording. Take a first hand look at our new 2400 wide channel recorder. See for yourself why we say it's the best performing direct writing recorder on the market today. Call your nearest Gould Sales Engineer to arrange a demonstration. Or write Gould Inc., Instrument Systems Division, 3631 Perkins Avenue, Cleveland, Ohio 44114. Or Kouterveldstraat 13, B 1920 Diegem, Belgium.

GOULD

On Reliability and a Pound of Flesh

The life's blood of an electrocardiograph is the chart that flows through it.

Assurance that the recording is totally reliable depends, in part, on the quality of the chart itself.

Charts, as provided by the instrument maker, afford this assurance to a maxima ... because they are designed as an integral part of the instrument.

Charts, as provided by others, are imitations at best. They may save a few pennies, but not without risk of shedding a "drop of reliability".

This message was prepared in the interest of better instrument performance by ...

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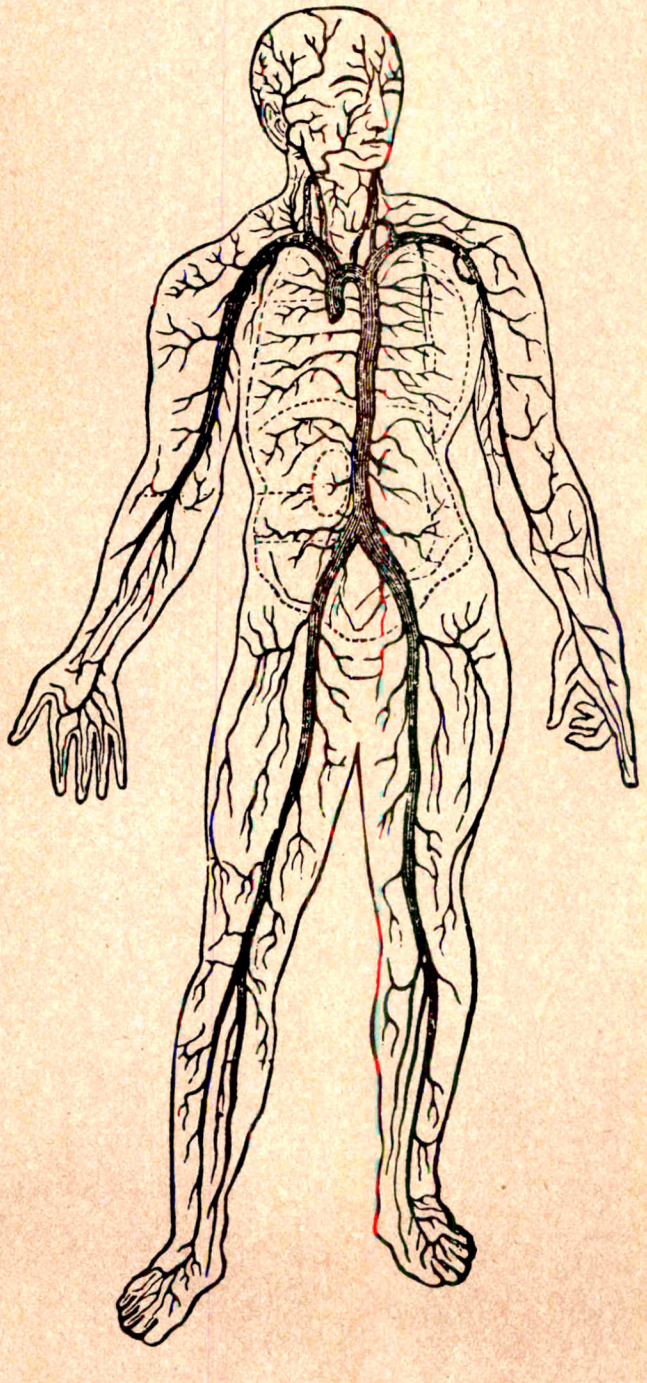
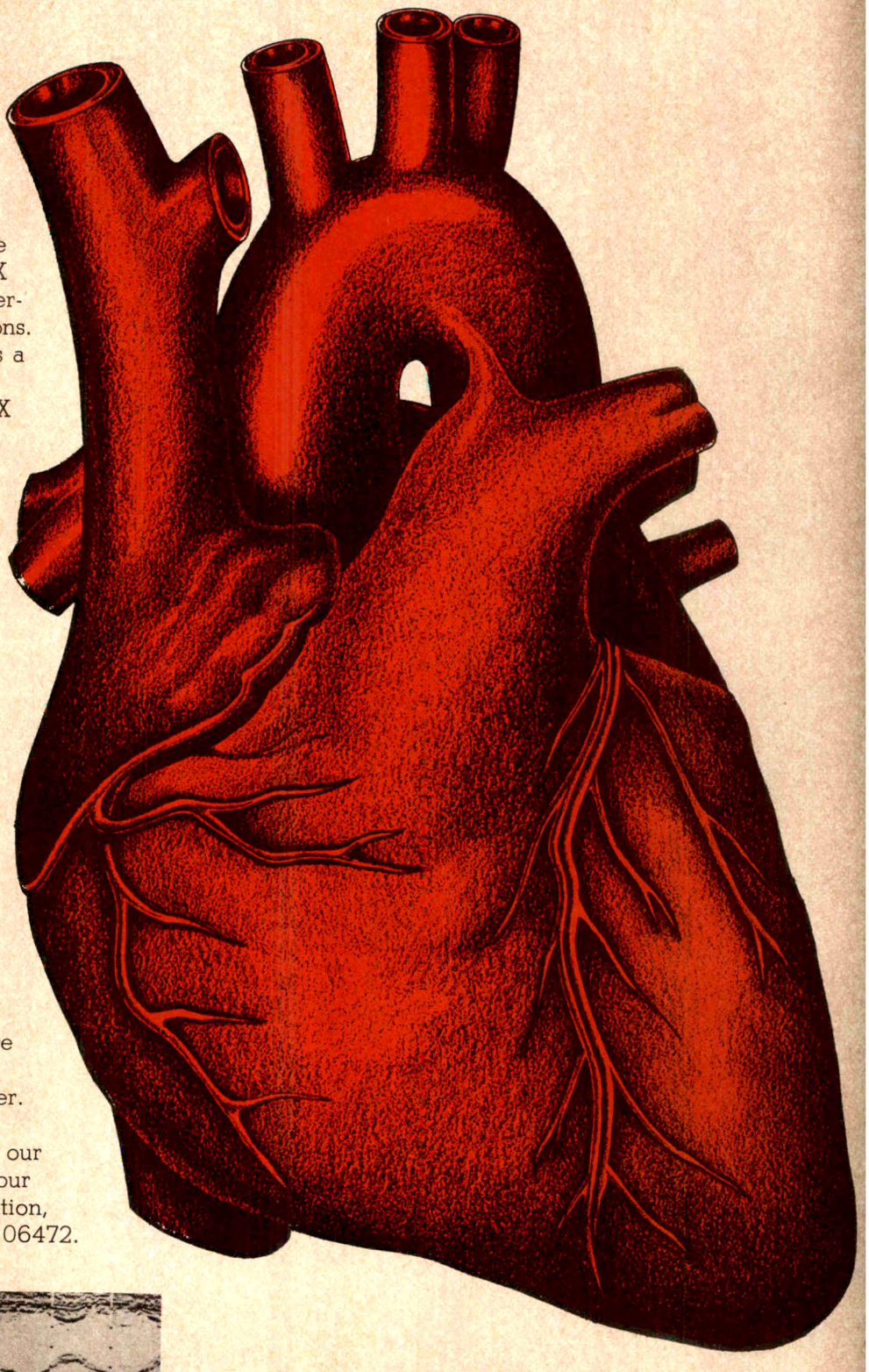


Echocardiography



Picker ultrasonic cardiography systems detect and display every heart malfunction currently identifiable by diagnostic ultrasound. What's more, the flexibility built into Echoview™ X heart systems is a solid base for perfecting new cardiology applications.

With Echoview X, flexibility is a prime concern.

For example, since Echoview X systems are modular, additions can be made economically as your needs expand.

Echoview X systems accommodate a full range of transducers from 1 mHz to 10 mHz. This is especially valuable in pediatrics including neonatal studies.

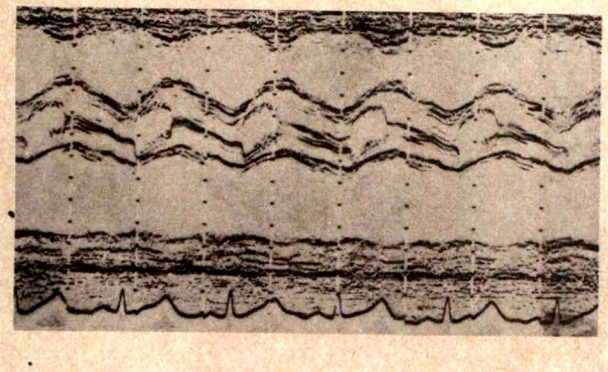
To compensate for varying requirements in heart studies, Echoview's strip chart recorder is capable of speeds up to 200mm per second.

And with Picker Echoview X you get high resolution and faithful reproduction of recorded data because Picker uses fiber optics and superior electronics.

Taken as a whole the Echoview X achieves maximum system flexibility for maximum performance efficiency.

No other system today is better. See for yourself.

We'll be happy to demonstrate our flexibility in equipment and in our service. Contact Picker Corporation, 12 Clintonville Rd., Northford, CT 06472.



PICKER®
ONE OF THE C.I.T. COMPANIES

now, one station does it all... collects ECG data, computes, analyzes, prints report

in minutes, at bedside, without central computer or telephone tie-ins

The Roche Mobile Computerized ECG Station contains its own minicomputer, recorder, and printer. It can eliminate the routine work associated with the reading of normal ECG's. It is highly accurate, classifying correctly 95-98% of normal ECG's, 85% of abnormals.[1] It is fast, supplying a computer printout based on the widely accepted USPHS program within a minute after readings are taken.

There is a high degree of patient safety. Also, the Roche Station signals the operator immediately when tracings are being taken incorrectly or are of poor quality; it identifies interpretations that may be incomplete or equivocal.

The Roche Mobile Station offers considerable savings over telephone tie-in ECG systems and yet avoids the extensive investment required for a dedicated central computer. Economic feasibility studies and additional information are available from Roche.

1. Hochberg, H. M., et al.: Automatic electrocardiogram analysis in rapid mass screening. *Arch. Environ. Health* 15:390-398, 1967.

For more information

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ROCHE

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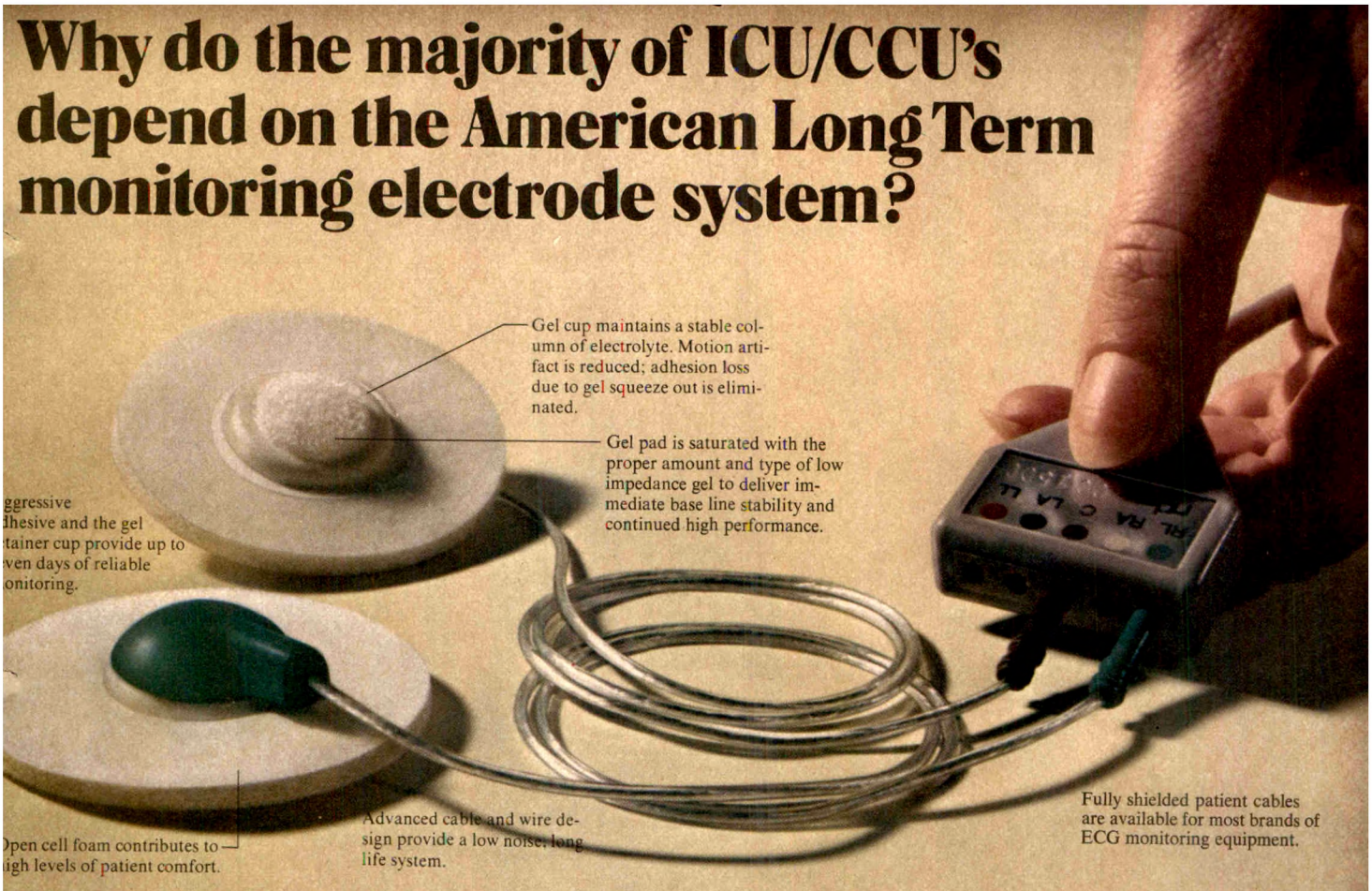
Why do the majority of ICU/CCU's depend on the American Long Term monitoring electrode system?



This is the system that has established new standards for high performance in long term ECG monitoring.

Designed for single patient use, the self-adhering silver/silver chloride electrode is pregelled with the correct amount of proper electrolyte. Adhesion loss and electrolyte evaporation are virtually eliminated by the gel retaining cup. The results: Immediate base line stability and better long term performance than any other electrode —reusable or disposable—is capable of delivering.

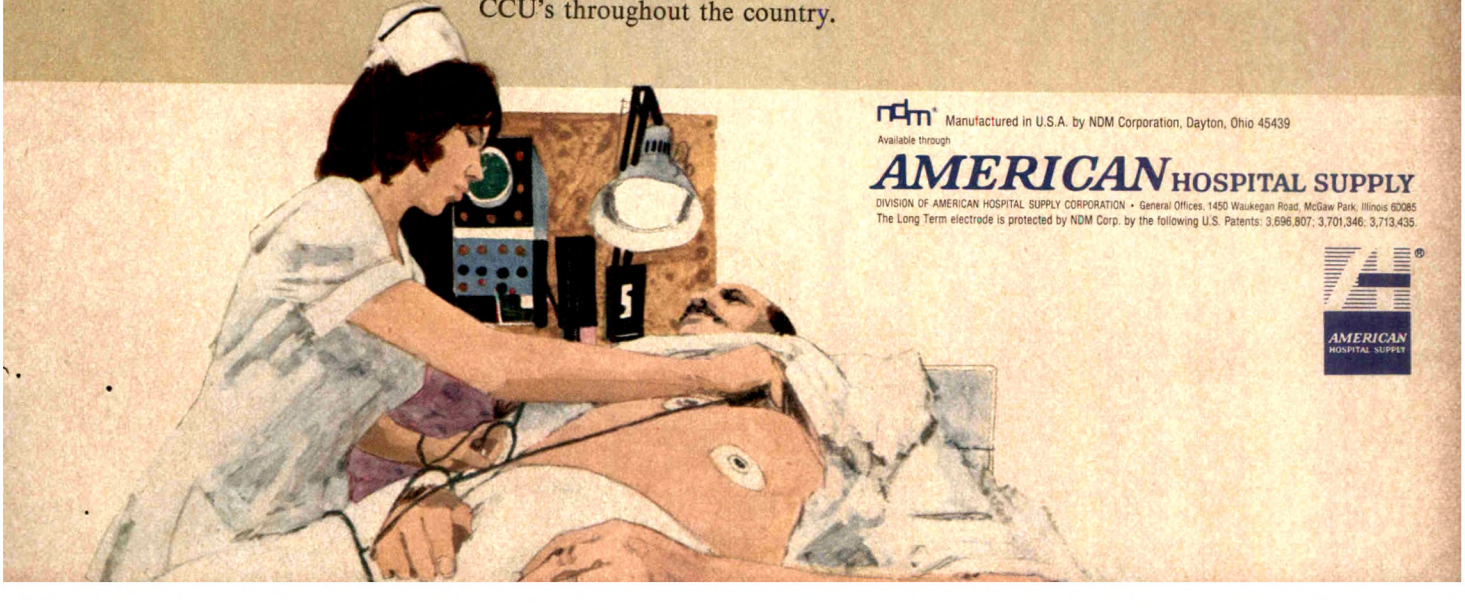
Open cell foam complements the electrode's mild gel formulation and low profile to enhance patient comfort. When used as directed, American's Long Term Electrode provides from five to seven days of continuous, accurate monitoring . . . with no discomfort to the patient.

This advanced electrode, used with the appropriate American leadwire and cable, is fully compatible with your present ECG equipment.

A clinical trial will show you why the American Long Term Electrode system is the overwhelming choice of ICU/CCU's throughout the country.

Please contact your American Hospital Supply or NDM representative and ask for:

- A demonstration of the system's benefits.
- A no obligation clinical trial. American will supply electrodes, leadwires and cables to adapt to your present monitoring equipment during the trial period.
- A total inservice for your staff.
- Information about our nationwide technical support program.



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Available through

AMERICAN HOSPITAL SUPPLY

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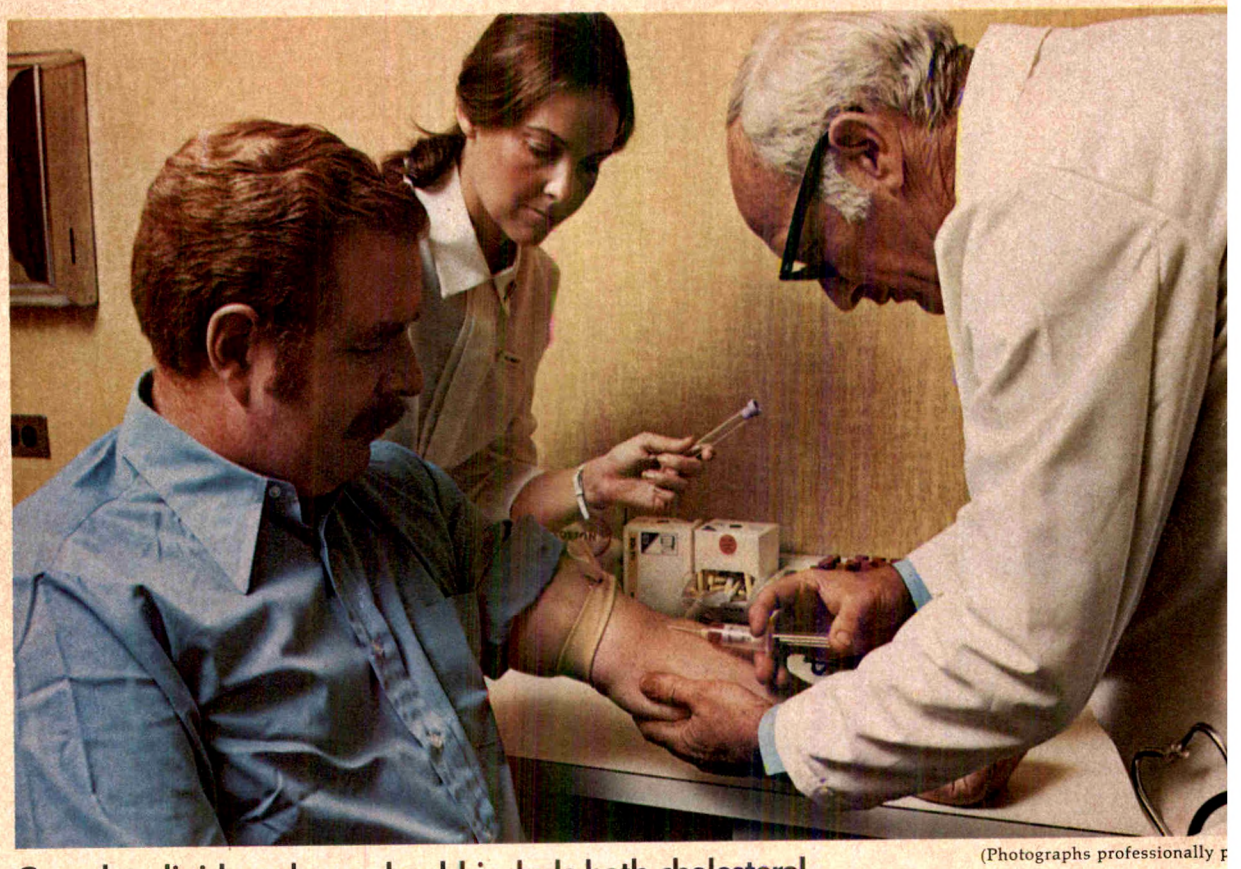
The Long Term electrode is protected by NDM Corp. by the following U.S. Patents: 3,696,807; 3,701,346; 3,713,435.

AMERICAN HOSPITAL SUPPLY

"Hyperlipidemia is one of several factors I searc



(Photographs professionally p

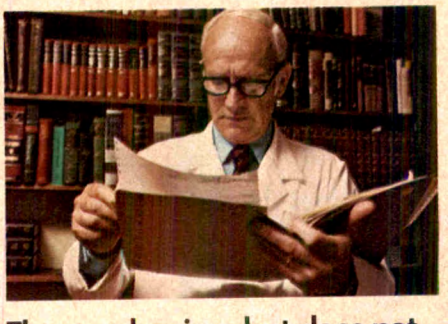
Complete lipid work-up should include both cholesterol and triglyceride determinations

Testing for both lipids—rather than just for cholesterol alone—increases the chances of detecting hyperlipidemia from 60% to over 95%.[2]

Lab results indicate pattern of lipid abnormality

When initial determinations of fasting serum cholesterol and triglyceride levels indicate the presence of hyperlipidemia, the pattern of the lipid abnormality should also be determined.[3]

When lipid elevations are confirmed, underlying disease states that may alter lipid metabolism should be ruled out through history, physical examination, and appropriate laboratory tests. Effective treatment of these pathologic conditions, if they exist, will often return the elevated lipids to a normal range. In the absence of an underlying cause, elevated lipid levels indicate a primary hyperlipidemia.



Therapy begins–but does not necessarily end–with specific dietary recommendations

Diet (specific for the lipid abnormality) is the starting point in the management of primary hyperlipidemia, and in the relatively rare Type I hyperlipoprote emia it is the *only* therapy since curre available drugs are ineffective. But ir the drug-responsive types (Types IIa IIb, III, IV and V) diet alone may fail lower lipids adequately.

Drug therapy is often necessary as an adjunct to

Convincing the asymptomatic hyper demic patient to give up his favorite foods for benefits he may not feel is, best, a difficult task. Even under care fully monitored dietary regimens, lip reductions may be inadequate.[4] For t reasons it is often necessary to add a antilipemic agent to the dietary regi to produce a significant reduction in serum lipids.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

or and vigorously treat."[1]

long with early hypertension, excessive garette smoking and dietary indiscre-ons, it is one of the few manifestations modern society that an individual ysician can attempt to control."[1]

This is how one clinician views hyper-idemia—a condition widespread in merica today. The treatment he speaks often calls for a dietary regimen spe-fic for the lipid abnormality *plus* an tilipemic agent. And since many hy-rlipidemic patients exhibit elevations *both* cholesterol and triglycerides, ey need a drug such as ATROMID-S lofibrate), which has the ability to wer *both* lipids.

tromid-S significantly reduces choles-rol and triglycerides—even in diet-sistant patients

ATROMID-S as an adjunct to diet has proven record of effectiveness in lower-g serum elevations of both cholesterol d triglycerides.

Cholesterol levels above 250 mg.% ve decreased as much as 35%, d reductions up to 50% have been ported.[5-8] Triglyceride levels above 0 mg.% have decreased as much as %, and reductions up to 90% have en reported.[5,8] Patients resistant to et alone have also experienced signifi-nt lipid lowering on ATROMID-S.

Although most hyperlipidemic pa-nts are asymptomatic, a small number ay exhibit skin lesions or xanthomas. egression of xanthomatous lesions with TROMID-S visually demonstrates the efficacy of this lipid-lowering agent. In some patients xanthomas disappear completely. In others the size and number of lesions are reduced.

Continuous treatment, maintenance of daily dosage vital to long-term control

Reliable cholesterol- and triglyceride-lowering effect is usually sustained as long as ATROMID-S treatment is uninterrupted. This ability to maintain control of serum lipids for extended periods is of primary importance in treating a disorder as persistent as hyperlipidemia.

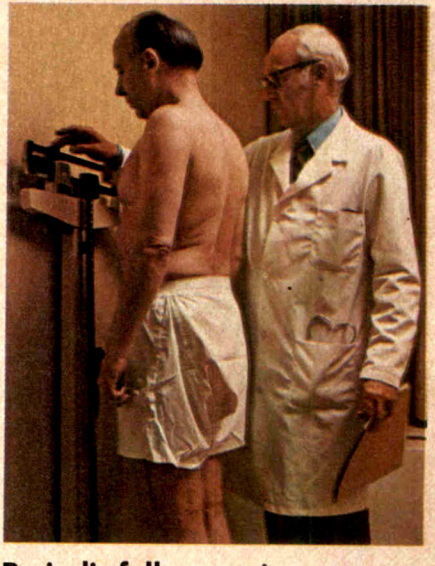
ATROMID-S is effective in a simple, well-accepted regimen that patients can stay with. Initial *and* maintenance dosage is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. To maintain continuous control of lipid levels, therapy should be uninterrupted.

The lipid-lowering effect of ATROMID-S is usually noted during the first month of therapy. The higher the initial level, the greater the lipid reduction likely to occur.

If response is inadequate after three months of therapy, the drug should be discontinued. However, if xanthoma tuberosum is present, treatment should continue for longer periods (even up to one year) provided there is a reduction in the size and/or number of the xanthomas.

10 years of successful overall clinical experience with Atromid-S

Throughout more than ten years of widespread use, ATROMID-S has proven to be an effective and very well-tolerated drug. However, before prescribing, you should be thoroughly familiar with the possible adverse reactions as well as with the precautions and warnings described on the last page of this advertisement.



Periodic follow-up important

Once blood lipids have been stabilized at normal levels on a regimen of diet and ATROMID-S, the patient should be examined and his blood lipids tested every two to three months during the first year or so. If stabilization at such lower levels is maintained over this period, the intervals between measurements can be lengthened.

Atromid-S®

Brand of clofibrate

helps control the lipid factor in your patient's profile

Ayerst®

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

See last page of advertisement for prescribing information.

Atromid-S® (clofibrate)

helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone

Initial and maintenance dosage: 2 Gm. daily (four capsules), in divided doses. Some patients may respond to a lower dosage.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. Hepatic biopsies are usually within normal limits. These effects are usually reversible when the drug is discontinued. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. *Maintenance:* Same as for initial dosage. **Note:** In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. La Bree, J., M.D. (Director of Medical Education, St. Mary's Hosp., Minneapolis, Minn.): Unraveling the Metabolic Mysteries Affecting Diagnosis and Therapy, Ayerst Laboratories, 1972, p. 13. 2. Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, New York, Plenum Press, 1969, vol. 4, p. 314. 3. Levy, R. I., in Conn, H. F.: Current Therapy 1973, Philadelphia, Saunders, 1973, p. 267. 4. Parsons, W. B., Jr.: Clin. Med. *78*:15 (Nov.) 1971. 5. Gelfand, M. L., and Garber, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. 6. Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. 7. Zelis, R., *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. 8. Levy, R. I., and Fredrickson, D. S.: Am. J. Cardiol. 22:576 (Oct.) 1968.

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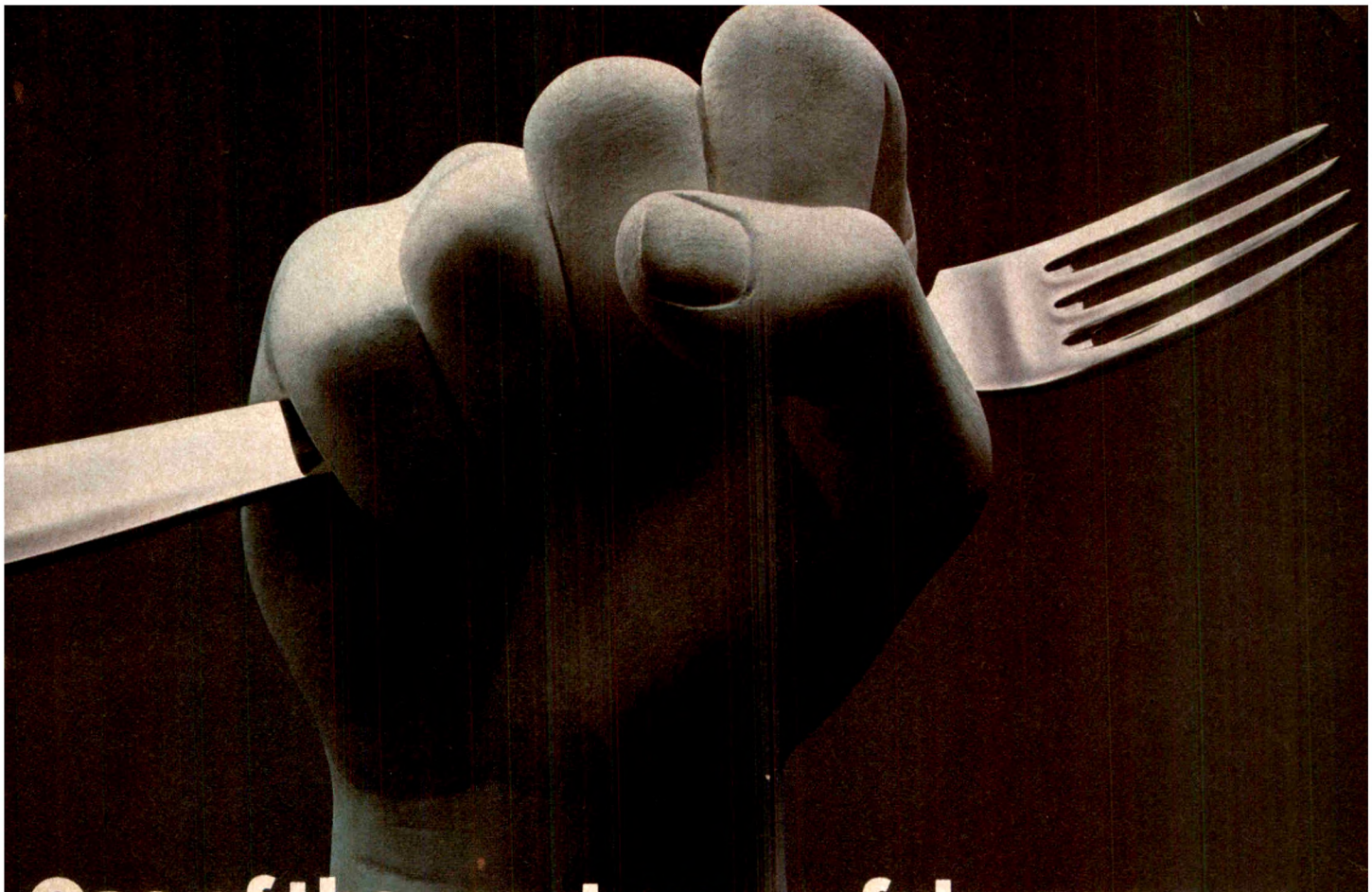
New York, N.Y. 10017



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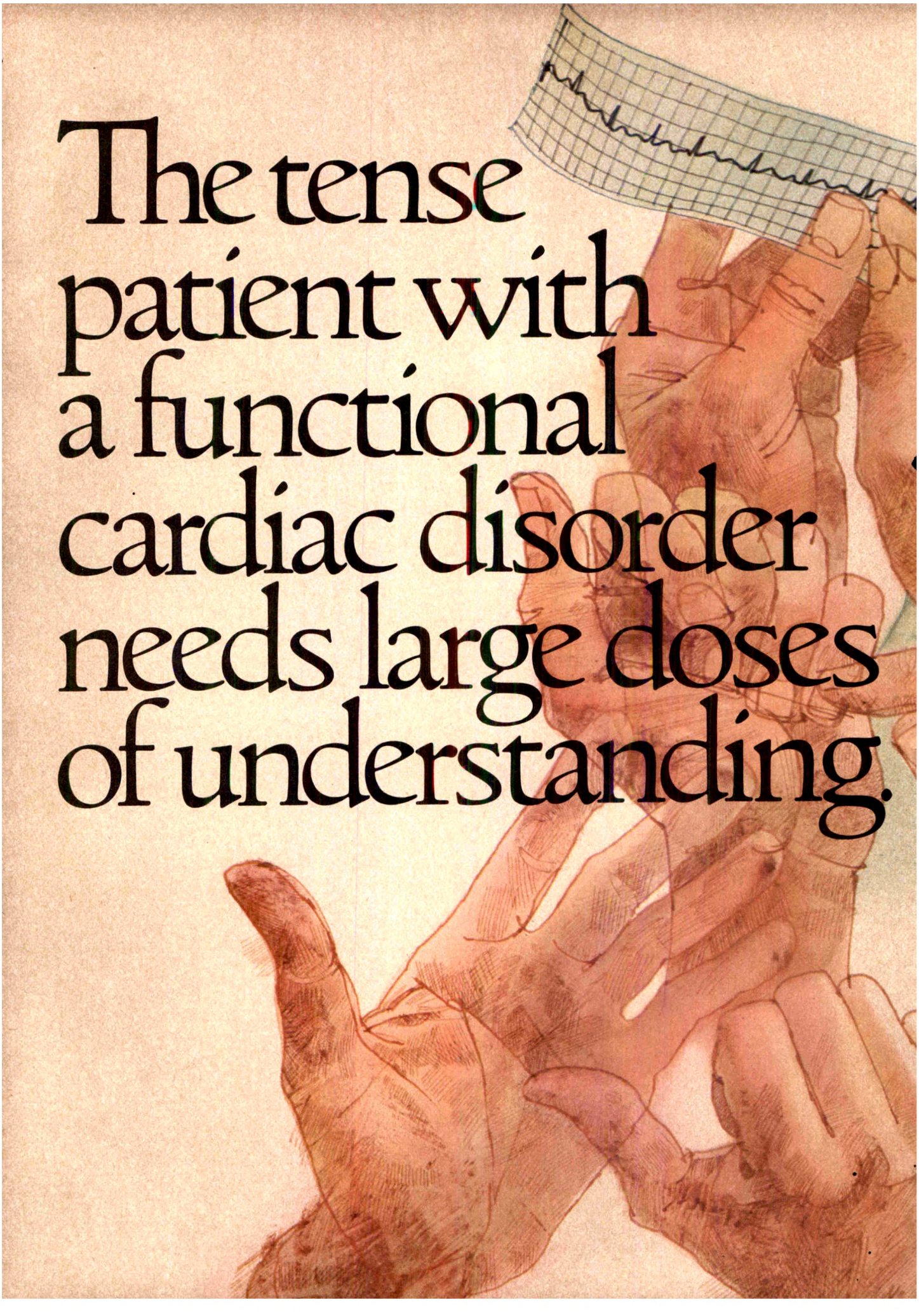
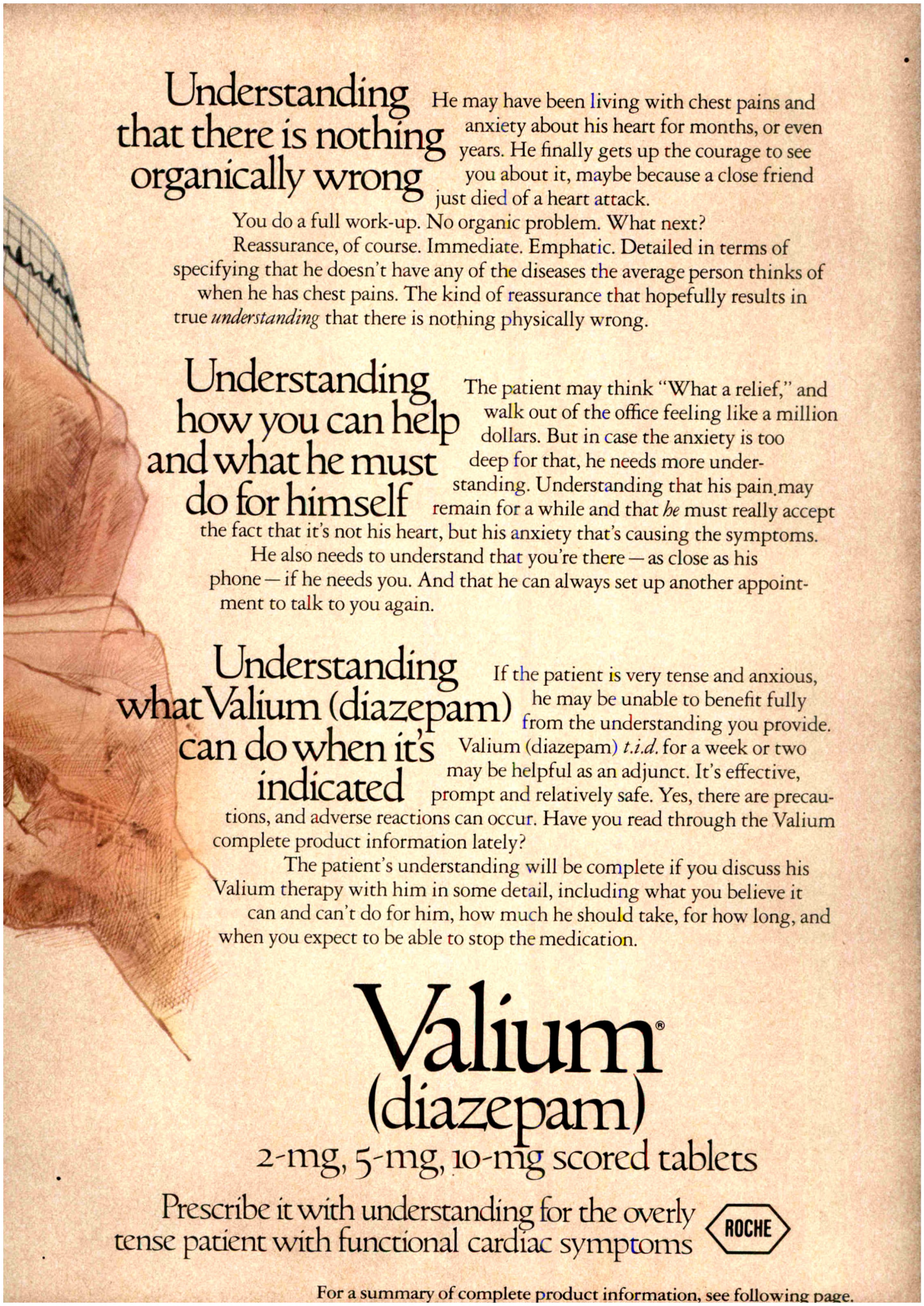
A low saturated fat/low cholesterol diet can be effective, easy to maintain and delicious with the help of Fleischmann's® Margarine and Egg Beaters,™ Fleischmann's cholesterol-free egg substitute.

Of all leading margarines, only Fleischmann's is made from 100% corn oil. And clinical tests show corn oil is unsurpassed in lowering serum cholesterol levels. Fleischmann's Margarine brings that corn oil goodness and delicious taste to your patients' diets. And Egg Beaters, Fleischmann's cholesterol-free egg substitute, lets patients enjoy the taste and nutrition of eggs, but no cholesterol. Yes, Fleischmann's helps a butter-and-egg man enjoy a delicious, sensible diet that's low in cholesterol and saturated fat. We even have free recipe booklets to give patients lots of ideas on sensible eating. To receive your sample copy of "Dietary Control of Cholesterol" and "Cooking with Egg Beaters," write to Fleischmann's, P.O. Box 1538, Elm City, North Carolina 27898. Allow 4-6 weeks for delivery. Offer good only in U.S.A. while supply lasts. Address must include zip code. Void where prohibited.

Fleischmann's makes sensible eating delicious.

Fine products of *Standard Brands*


The tense
patient with
a functional
cardiac disorder
needs large doses
of understanding.



Understanding that there is nothing organically wrong

He may have been living with chest pains and anxiety about his heart for months, or even years. He finally gets up the courage to see you about it, maybe because a close friend just died of a heart attack.

You do a full work-up. No organic problem. What next?

Reassurance, of course. Immediate. Emphatic. Detailed in terms of specifying that he doesn't have any of the diseases the average person thinks of when he has chest pains. The kind of reassurance that hopefully results in true *understanding* that there is nothing physically wrong.

Understanding how you can help and what he must do for himself

The patient may think "What a relief," and walk out of the office feeling like a million dollars. But in case the anxiety is too deep for that, he needs more understanding. Understanding that his pain may remain for a while and that *he* must really accept the fact that it's not his heart, but his anxiety that's causing the symptoms.

He also needs to understand that you're there — as close as his phone — if he needs you. And that he can always set up another appointment to talk to you again.

Understanding what Valium (diazepam) can do when it's indicated

If the patient is very tense and anxious, he may be unable to benefit fully from the understanding you provide. Valium (diazepam) *t.i.d.* for a week or two may be helpful as an adjunct. It's effective, prompt and relatively safe. Yes, there are precautions, and adverse reactions can occur. Have you read through the Valium complete product information lately?

The patient's understanding will be complete if you discuss his Valium therapy with him in some detail, including what you believe it can and can't do for him, how much he should take, for how long, and when you expect to be able to stop the medication.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg scored tablets

Prescribe it with understanding for the overly tense patient with functional cardiac symptoms

ROCHE

For a summary of complete product information, see following page.

Prescribe it with understanding for the overly tense patient with functional cardiac symptoms

Valium®
(diazepam)
2-mg, 5-mg, 10-mg scored tablets

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 100; Prescription Paks of 50, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

IN ANGINA*: **ACTS WITH SUBLINGUAL SPEED**

CHEWABLE SORBITRATE® 5MG.
ISOSORBIDE DINITRATE

As with sublingual ISDN:
acts in 2 minutes for therapeutic use...
acts up to 2 hours for prophylaxis.

In addition:
chewing action helps distribute nitrate over a larger mucosal area.

SUMMARY OF
PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.
Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.
Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.
Dosage and Administration: Route: Sublingual, oral and chewable tablets.
Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:
Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.
Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.
It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
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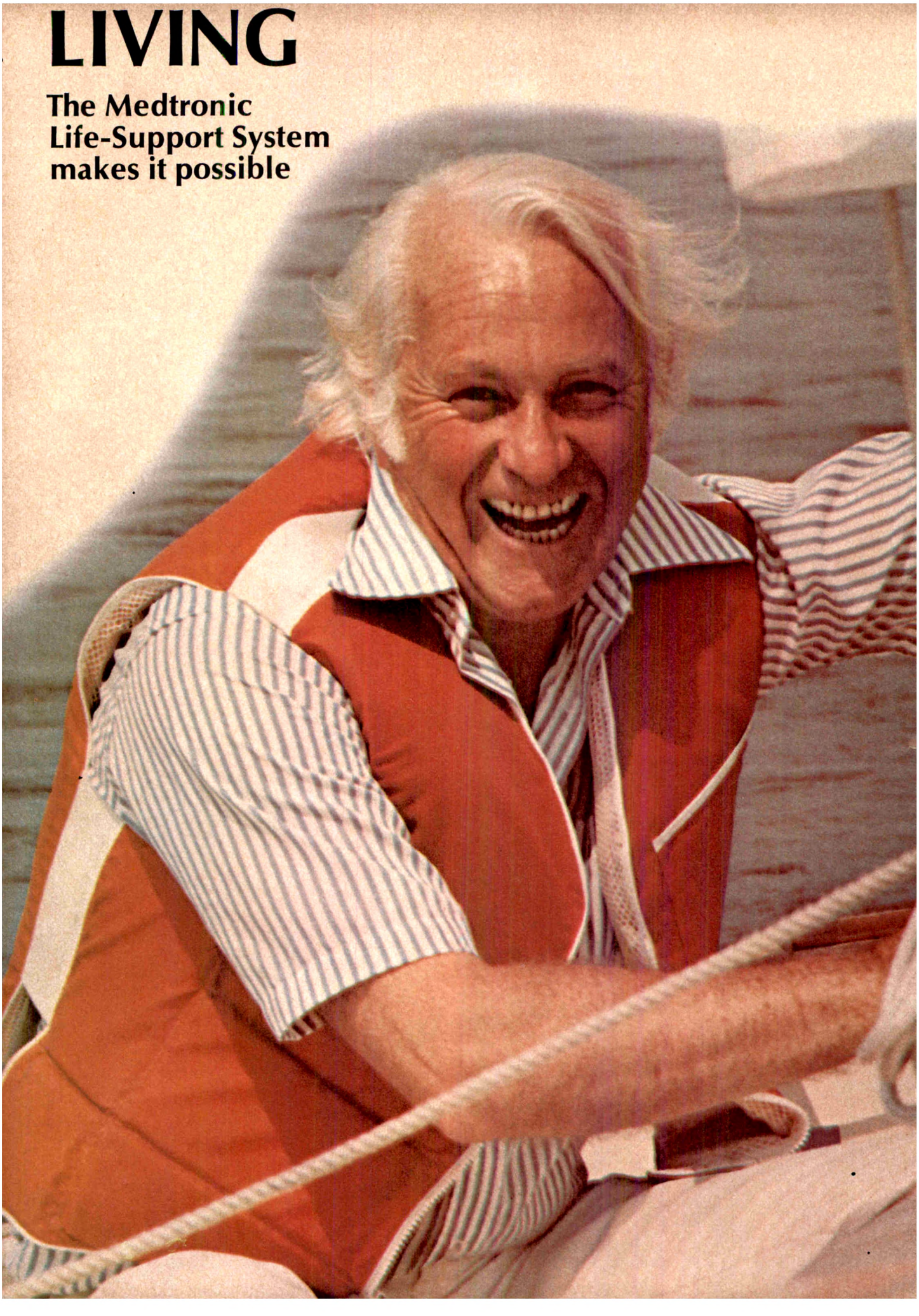
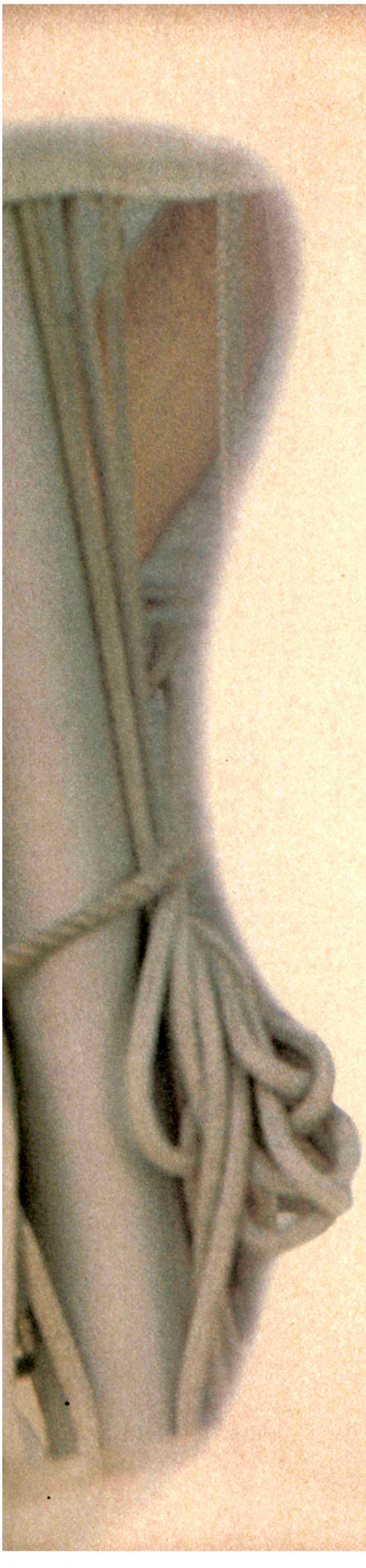
Wilmington, Delaware 19897

LIVING

The Medtronic Life-Support System makes it possible





A coordinated system providing continuous control of the pacemaker patient from pre-implant care to post-implant follow-up

STABILIZED PRIOR TO SURGERY *with a Medtronic External Pacemaker.*

CONTROLLED DURING IMPLANTATION *by the Medtronic Pacing System Analyzer.*

PACED *by a Medtronic pulse generator and lead.*

FOLLOWED AFTER IMPLANTATION *with the Medtronic TeleTrace™ Telephone EKG System or by the Medtronic Pacemaker Pulse Monitor.*

THE PACEMAKER GIVES YOU MORE THAN JUST A PACEMAKER

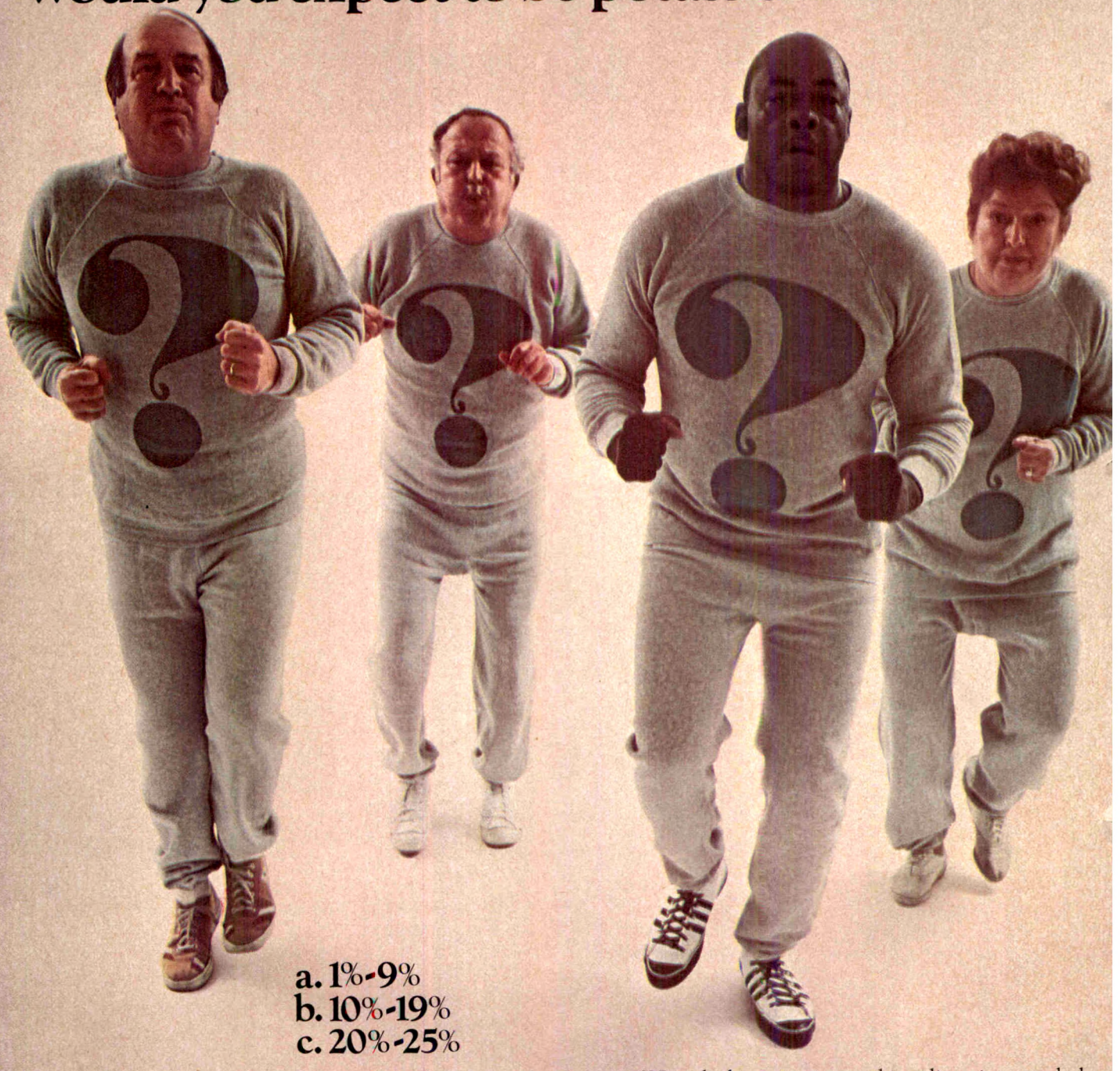
Originally, when Medtronic pioneered the development of pacemaker technology, there was only the pacemaker. Today, there is more. Much more. Today, the pulse generator is only one part of a total life-support system. It's the sort of system that can assure your patient optimum performance from the implanted unit plus the benefits of a fuller, more complete life.

Medtronic provides you with a variety of well-integrated equipment. Equipment designed to be part of a total life-support system. *Equipment that gives you continuity in the close control of your pacemaker patients. The innovative thinking that led to the development of such a total life-support system is just one of the many reasons why Medtronic* is *the pacemaker in pacemaking.*

Medtronic representatives are strategically located throughout the world. For more complete product information contact the representative nearest you.

Medtronic
THE PACEMAKER
IN PACEMAKING

What percent of your diuretic patients would you expect to be potassium deficient?



a. 1%-9%
b. 10%-19%
c. 20%-25%

Serum electrolyte determinations on 627 ambulatory patients taking diuretics revealed that *nearly one in four* (23.9%) were hypokalemic (serum potassium <3.5 mEq. per liter), and 4.3% were hypochloremic (serum chloride <95 mEq. per liter) as well as hypokalemic.

Too often patients cannot consume enough potassium by diet alone to ensure adequate replacement.

That's where *Kaochlor*® (potassium chloride) comes in—a pleasant-tasting, citrus-flavored liquid which contains 20 mEq. each of potassium and chloride per 15 ml. It should be diluted with citrus juices, citrated soft drinks or water. And dosage is flexible, to satisfy the potassium and chloride needs of each individual patient.

Kaochlor® for the one in four.
(potassium chloride)

BRIEF SUMMARY

KAOCHLOR® (Potassium Chloride)
10% LIQUID

Description: Each 15 ml. (tablespoonful) supplies: 20 mEq. each of elemental potassium and chloride (as potassium chloride, 1.5 Gm.) with sugar, saccharin and flavoring. Alcohol, 5%.

Actions: Potassium chloride supplement.

Indications: Hypokalemic-hypochloremic alkalosis and for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. It may be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, and hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease. If the basic disturbance produces metabolic acidosis, as in some renal tubular disorders, an organic salt such as potassium gluconate may be more advantageous.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Before prescribing, see complete prescribing information in the PDR or the individual package insert.

*Manner, R. J.; Brechbill, D.O.; DeWitt, K.: Prevalence of Hypokalemia in Diuretic Therapy. Clin. Med. 79:15 (Nov.) 1972.

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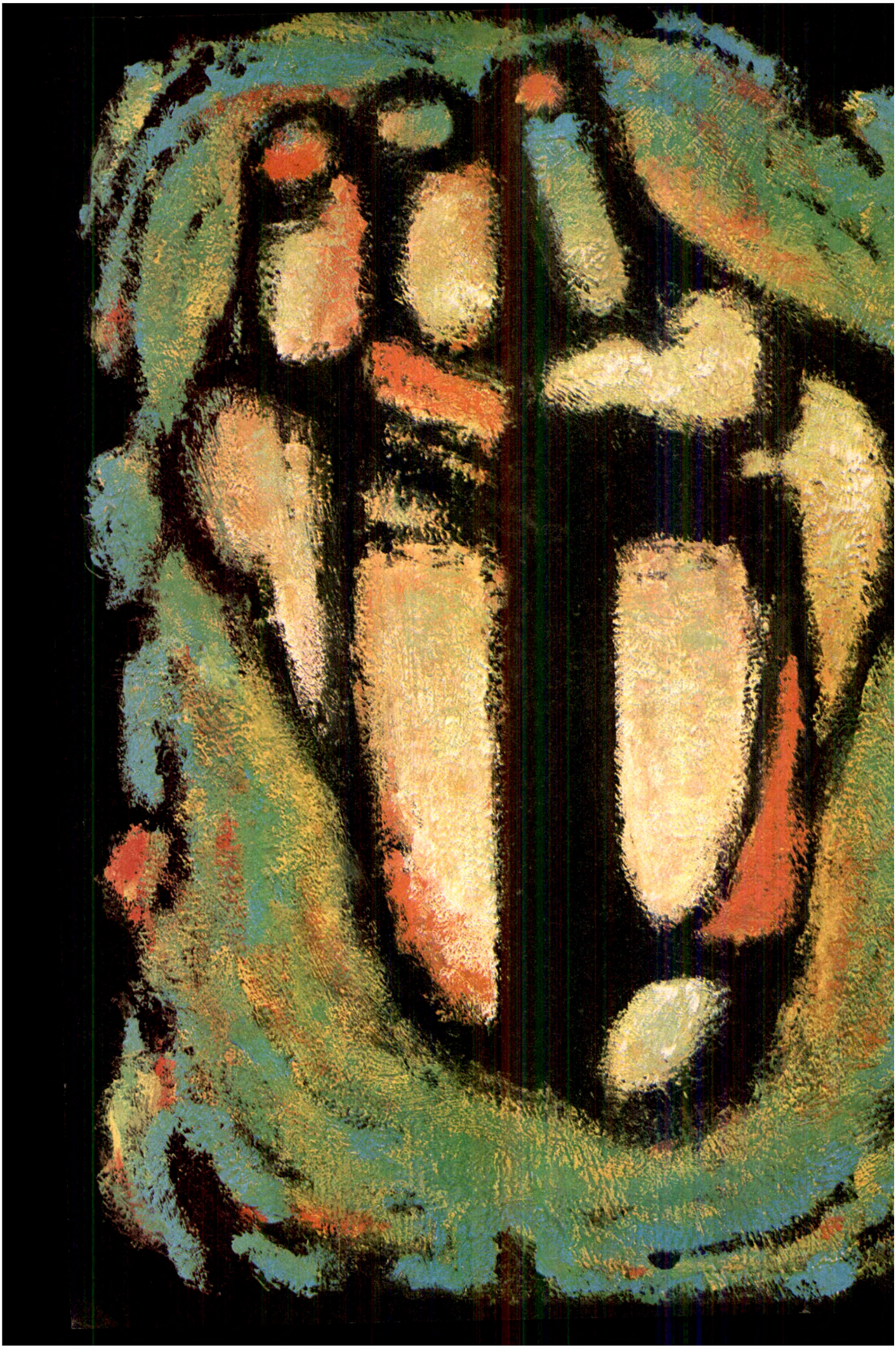


The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Give enough, long enough—The recommended dosage: 50 mg t.i.d. at least one hour before meals for several weeks or longer.

Persantine® Tablets of 25 mg
dipyridamole

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

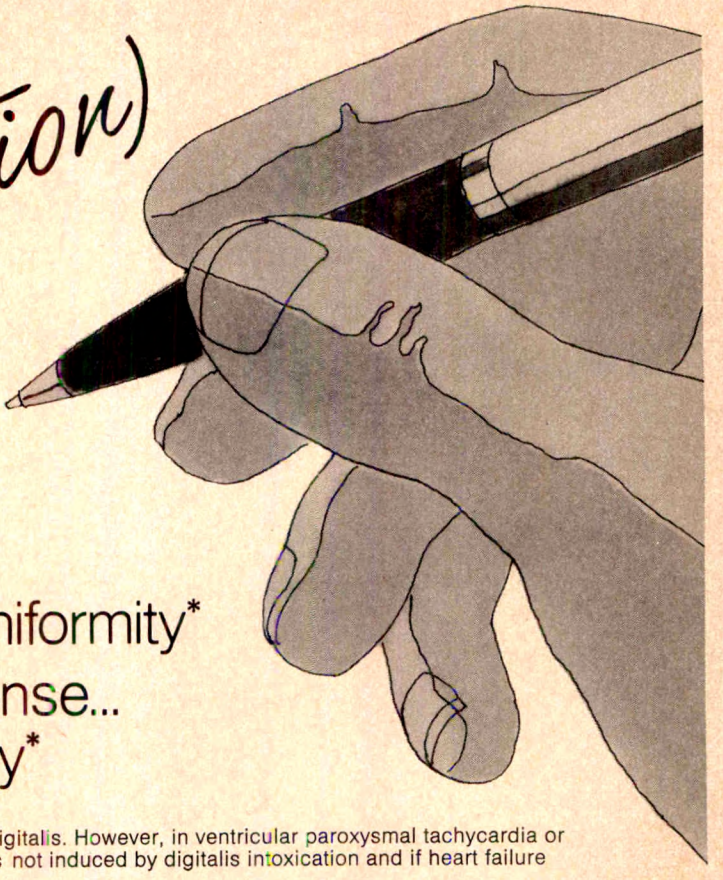
Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, N.Y. 10523

One of a series of paintings of the heart in the style of well-known artists.

The Heart... in the style of Georges Rouault (1871-1958)

Heavily emphasized outlines and brilliant swaths of color characterize the style of this artist. He preferred religious themes and created outstanding stained glass designs for churches.

Lanoxin [digoxin] (no substitution)



write it

precision quality control...

- assured tablet content uniformity*

predictable patient response...

- proven biologic availability*

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

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CLINICAL STUDIES

Mechanism of Left Ventricular Outflow Obstruction in Patients with Obstructive Asymmetric Septal Hypertrophy (Idiopathic Hypertrophic Subaortic Stenosis)

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Left ventricular outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis or obstructive asymmetric septal hypertrophy is due to abnormal forward motion during systole of the anterior mitral leaflet. To determine why some patients with this disease have left ventricular outflow obstruction whereas others do not, we studied a large number of patients with asymmetric septal hypertrophy using both one- and two-dimensional echocardiography. In 100 patients with asymmetric septal hypertrophy and 22 normal subjects, mitral valve position at the onset of systole was quantitated by measuring the distance from the ventricular septum to the mitral valve and the distance from the mitral valve to the posterior left ventricular wall. None of the normal subjects and only 3 (6 percent) of 51 patients with nonobstructive asymmetric septal hypertrophy had a septal-mitral valve distance of less than 20 mm compared with 23 (66 percent) of 35 patients with obstructive asymmetric septal hypertrophy. Moreover, the mitral valve at the onset of systole was actually positioned forward in the left ventricular cavity. Two-dimensional studies in 11 patients with obstructive asymmetric septal hypertrophy revealed that contraction of the malaligned papillary muscles did not cause the abnormal forward mitral valve motion. We propose that the left ventricular outflow obstruction in patients with obstructive asymmetric septal hypertrophy occurs as a result of two factors: (1) narrowing of the left ventricular outflow tract at the onset of systole, and (2) hydrodynamic forces generated by contraction on the left ventricle.

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Angiographic and echocardiographic observations in the mid- to late 1960's suggested that left ventricular outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis[1] was due to systolic apposition of the anterior mitral leaflet and the asymmetrically hypertrophied ventricular septum.[2–9] Definitive evidence substantiating this concept was obtained recently by the demonstration of a highly significant correlation between an echocardiographically measured obstruction index (computed from the duration and degree of systolic narrowing of the left ventricular outflow tract between the anterior

mitral leaflet and ventricular septum) and the simultaneously determined outflow gradient measured at cardiac catheterization.[10] However, it has also become apparent recently that patients with classic idiopathic hypertrophic subaortic stenosis represent only one part of a spectrum of disease that has asymmetric septal hypertrophy as its characteristic feature[11–14]; most patients with asymmetric septal hypertrophy either do not have left ventricular outflow obstruction or have it only after provocative maneuvers.[11–19] To determine why only some patients have such obstruction, we studied a large number of patients with asymmetric septal hypertrophy using one- and two-dimensional echocardiography. The results of this investigation, when combined with previous observations from our laboratory, suggest that outflow obstruction in this disease is a result of hydrodynamic forces and is not, as some have suggested, due to contraction during systole of malaligned papillary muscles.

Methods

One-Dimensional Echocardiographic Studies

Equipment: One-dimensional echocardiograms were obtained with an ultrasonic transducer (Aerotech, 2.25 megahertz, 1.25 cm diameter), an Ekoline 20A ultrasonic receiver and a Honeywell 1856 line scan recorder. The Ekoline receiver and Honeywell recorder were interfaced by way of a custom-built video processor. Signals were recorded on light-sensitive paper.

Patient population: One hundred adult patients with asymmetric septal hypertrophy were studied by one-dimensional echocardiography. In every case, the condition was documented echocardiographically and characterized by a ventricular septum at least 1.3 times the thickness of the posterobasal left ventricular free wall.

a. Patients with cardiac catheterization studies (classification): Cardiac catheterization data were available in 67 of the 100 patients. In all 67 patients the left ventricular outflow gradient was recorded first when the patient was supine and in a basal condition and then during or after several provocative maneuvers (for example, a premature ventricular contraction, a Valsalva maneuver or infusion of isoproterenol). With use of these data, patients were classified into the following three groups on the basis of the left ventricular outflow pressure gradient: (1) *obstructive group* (gradient at rest, provocable gradient well in excess of 50 mm Hg); (2) *provocable group* (no resting gradient, provocable gradient greater than 30 mm Hg and in most instances exceeding 50 mm Hg); and (3) *nonobstructive group* (no resting gradient, peak provocable gradient less than 30 mm Hg). Of the 67 patients, 35 were classified in the obstructive, 10 in the provocable and 22 in the nonobstructive group (as determined by cardiac catheterization data alone).

The degree of obstruction was estimated echocardiographically[10] and compared with catheterization data in each of these 67 patients (nonsimultaneous studies). Thirty-two of 35 patients with resting outflow obstruction had an echocardiographic obstruction index indicating outflow obstruction compared with only 1 of 22 patients with nonobstructive disease and 0 of 10 patients with provocable disease. Thus, in 63 of 67 patients, the echocardiographic and catheterization data were consistent. The four exceptions were patients who had undergone catheterization studies before 1964. In all four cases, physical findings had changed between 1964 and the present and were now compatible with the echocardiographic data.[20] As a result, three patients initially classified as having obstructive disease by catheterization data alone were reclassified as having nonobstructive disease; one patient initially classified in the nonobstructive group was reclassified in the obstructive group. Thus, as finally grouped, 33 patients were considered to have obstructive, 10 provocable and 24 nonobstructive disease.

Some patients with right ventricular hypertension may have disproportionate septal thickening.[13,21] Such patients usually are easily identified on clinical grounds and should not be included in the spectrum of asymmetric septal hypertrophy. In this study, 23 of the 24 patients with catheterization studies and nonobstructive asymmetric septal hypertrophy had a right ventricular systolic pressure of less than 35 mm Hg. Asymmetric septal hypertrophy in these patients therefore cannot be ascribed to right ventricular hypertension.

b. Patients with catheterization studies (systolic mitral valve motion): As would be expected, all 33 patients with an obstruction index indicating a resting left ventricular gradient had marked systolic anterior motion of the mitral valve leaflets. Ten other patients also had abnormal systolic anterior motion, but this motion was much less prominent than in the patients in the obstructive group and was not sufficient to give an obstruction index compatible with a resting gradient. None of these 10 patients had a resting gradient at cardiac catheterization, but 8 of 10 (80 percent) did have a gradient exceeding 30 mm Hg with provocative maneuvers. Twenty-four patients had no evidence of abnormal systolic motion of the mitral leaflets. In only 2 of the 24 (8 percent) could a gradient greater than 30 mm Hg be provoked at catheterization. Thus, those patients with asymmetric septal hypertrophy who have an obstruction index indicating no resting gradient but an abnormal systolic anterior motion of the mitral leaflets are likely to have a significant gradient provoked at catheterization, whereas those with no abnormal systolic motion are unlikely to have significant provocable gradients.

c. Patients without catheterization studies (classification): In the 33 patients with asymmetric septal hypertrophy without catheterization data, classification was based on echocardiographic data alone.

Of the total of 100 patients (including those with and without catheterization studies), 51 were in the nonobstructive group, 14 in the provocable group and 35 in the obstructive group.

Mitral valve position: The position of the mitral valve in the ventricular cavity at the onset of systole was assessed in every patient. Mitral valve position was measured with the ultrasonic beam reflected from the tip of the mitral valve. Proper beam orientation was obtained by first visualizing both the anterior and posterior mitral valve leaflets simultaneously and then scanning perpendicular to the left ventricular outflow tract (that is, across the tip of the valve) until the maximal systolic motion of the anterior mitral leaflet was seen. Mitral valve position was quantitated by measuring the distance from the mitral valve (defined as the point of apposition of the anterior and posterior mitral leaflets at the onset of systole) to (1) the ventricular septum, and (2) the left ventricular free wall (Fig. 1). A mitral valve position ratio was computed by dividing the septal-mitral valve distance into the mitral valve-posterior wall

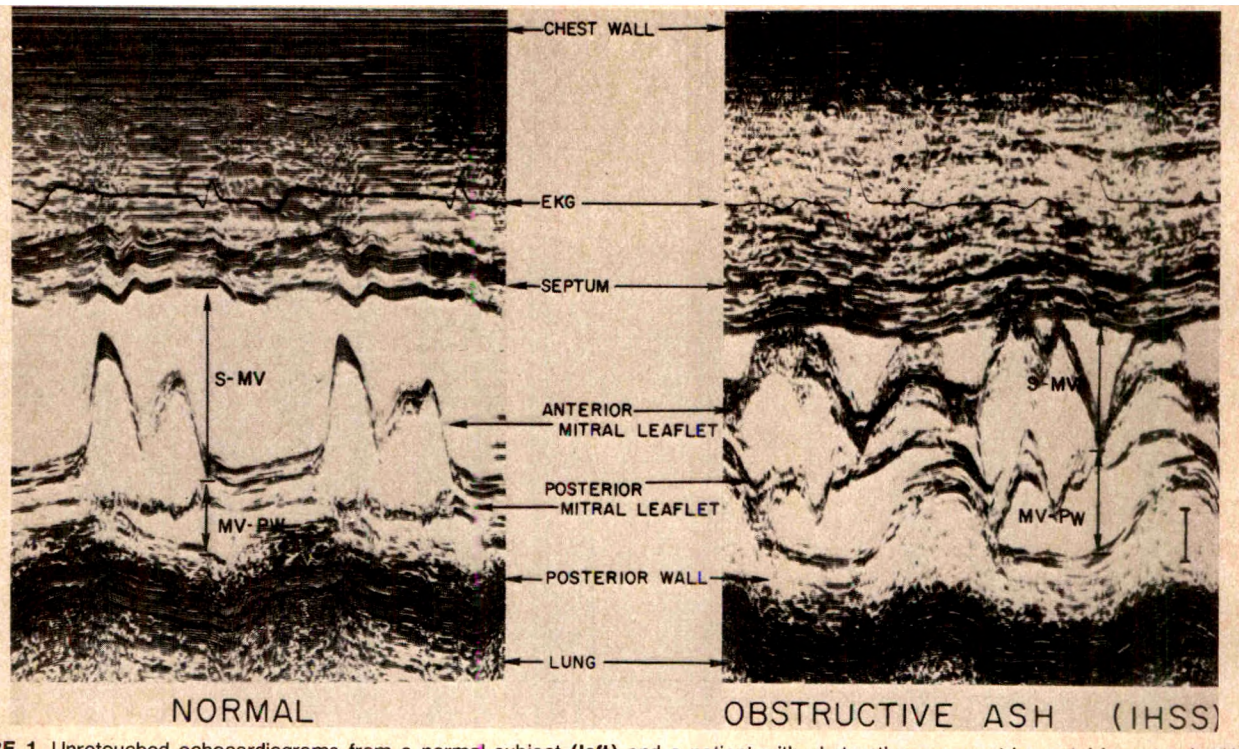

FIGURE 1. Unretouched echocardiograms from a normal subject **(left)** and a patient with obstructive asymmetric septal hypertrophy (ASH) **(right).** Compared with findings in the normal subject, septal-mitral valve distance (S-MV) is decreased in obstructive asymmetric septal hypertrophy whereas mitral valve-posterior wall distance (MV-PW) is increased, indicating that the mitral valve, at the onset of systole, is positioned forward in the left ventricular cavity. IHSS = idiopathic hypertrophic subaortic stenosis.

distance. In many patients, multiple echoes were recorded from the mitral valve during systole (Fig. 1). When this occurred, mitral valve position was defined from the point midway between the anterior and posterior mitral valve echoes at onset of systole.

Two-Dimensional Echocardiographic Studies

Equipment: Two-dimensional echocardiographic studies were obtained in real time using a custom-built mechanical sector-scanner consisting of a standard ultrasonic transducer (2.25 megahertz, 1.25 cm diameter, Aerotech transducer), an angle indicator and a small motor. The details of this system have been described previously. The transducer directs the ultrasonic beam into the chest and is angled rapidly through either a 30° or 45° arc at a rate of 15 cycles/sec. Each complete cycle results in the generation of two separate sectors (that is, one sector is produced as the transducer moves from left to right and another as it moves from right to left). Thus, 30 separate frames (or sectors) are produced per second, each one containing 100 individual ultrasonic data lines. The ultrasonic signals obtained by the scanner are electronically processed by an ultrasonic receiver (Ekoline 20A) and specially designed electronic circuits and displayed on a cathode ray tube. The two-dimensional images are recorded permanently with a closed-circuit television system. In this system, a television camera is focused on the cathode ray tube and the camera output recorded by a videotape unit. The videotapes obtained in this manner are used for subsequent analysis.

Patient selection: Eleven patients with obstructive asymmetric septal hypertrophy were studied by two-dimensional echocardiography. In every case, the condition had been demonstrated previously by one-dimensional echocardiography, and the degree of obstruction had been determined by both cardiac catheterization and one-dimensional echocardiography.

Study procedure: In each study, the sector scanner was oriented in two ways: (1) parallel to the left ventricular long axis, and (2) perpendicular to the left ventricular long axis. With both parallel and perpendicular orientation, particular care was used so that the papillary muscles, mitral valve, left ventricular outflow tract and ventricular septum were visualized.

Results

One-Dimensional Echocardiography

The mean septal-mitral valve distance was 34.6 mm in normal subjects, 19.6 mm in those with obstructive asymmetric septal hypertrophy, 22.0 mm in those with provocable and 27.4 mm in those with nonobstructive asymmetric septal hypertrophy (Fig. 2). The mean distances in the patients with asymmetric septal hypertrophy were significantly less than the distance in normal subjects ($P < 0.01$), and mean distances in those with obstructive and provocable disease were significantly less than that measured in patients with nonobstructive disease ($P < 0.01$). Twenty-three of 35 patients with obstructive disease (66 percent) had a septal-mitral valve distance of 20 mm or less compared with only 3 of 51 patients with nonobstructive disease (6 percent). The mean *mitral valve-posterior wall distance* was 9.8 mm in normal subjects and 20.0 mm in the obstructive, 19.4 mm in the provocable and 16.0 mm in the nonobstructive group (Fig. 2). These distances in pa-

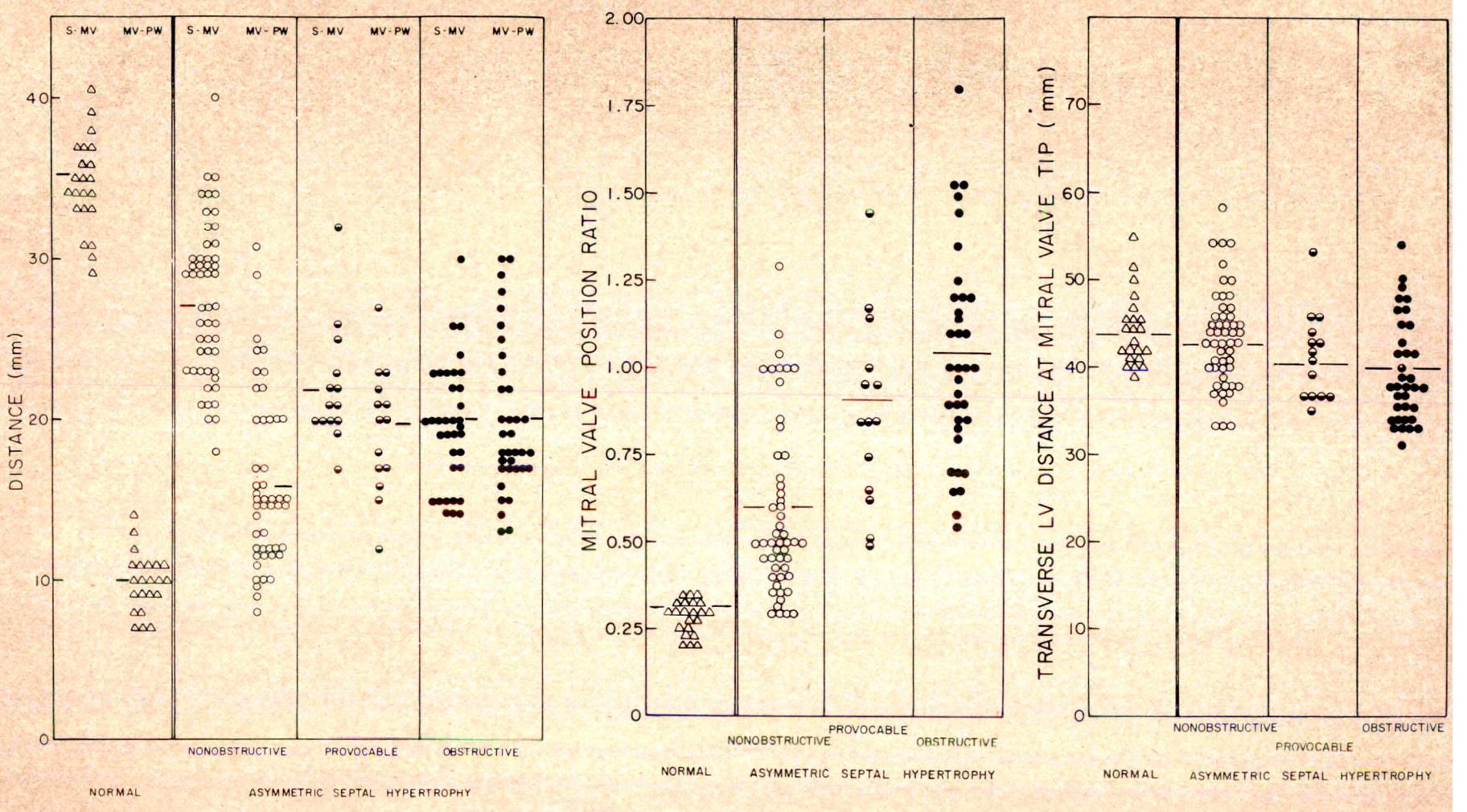

FIGURE 2 (left). Septal-mitral valve distance (S-MV) in millimeters is shown on the left of each panel and mitral valve-posterior wall distance (MV-PW) in millimeters is shown on the right for 22 normal subjects and 51 patients with nonobstructive, 14 with provocable and 35 with obstructive asymmetric septal hypertrophy.

FIGURE 3 (center). Mitral valve position ratio (calculated by dividing septal-mitral valve distance into mitral valve-posterior wall distance) for the same patients whose data are shown in Figure 2.

FIGURE 4 (right). Left ventricular transverse dimension in millimeters measured at the tip of the mitral leaflets for the same patients whose data are shown in Figures 2 and 3.

tients with asymmetric septal hypertrophy were all significantly greater than that of normal subjects ($P < 0.01$). The *mitral valve position ratio* (septal-mitral valve distance divided into the mitral valve-posterior wall distance) was 0.29 in normal subjects, 1.03 in obstructive asymmetric septal hypertrophy, 0.87 in provocable cases and 0.59 in nonobstructive cases (Fig. 3). These ratios were all significantly different from one another ($P < 0.01$).

The transverse dimension of the left ventricle at the level of the tip of the mitral valve was computed by adding the septal-mitral valve distance and the mitral valve-posterior wall distance. Transverse dimension averaged 44.2 mm in normal subjects and 39.7 mm in obstructive, 41.4 mm in provocable and 43.4 mm in nonobstructive asymmetric septal hypertrophy (Fig. 4). Compared with data in normal subjects, the mean left ventricular transverse dimension of the patients with obstructive disease was significantly reduced ($P < 0.01$); it was not significantly reduced in either the provocable ($P > 0.05$ but < 0.10) or nonobstructive group ($P > 0.5$). The mean

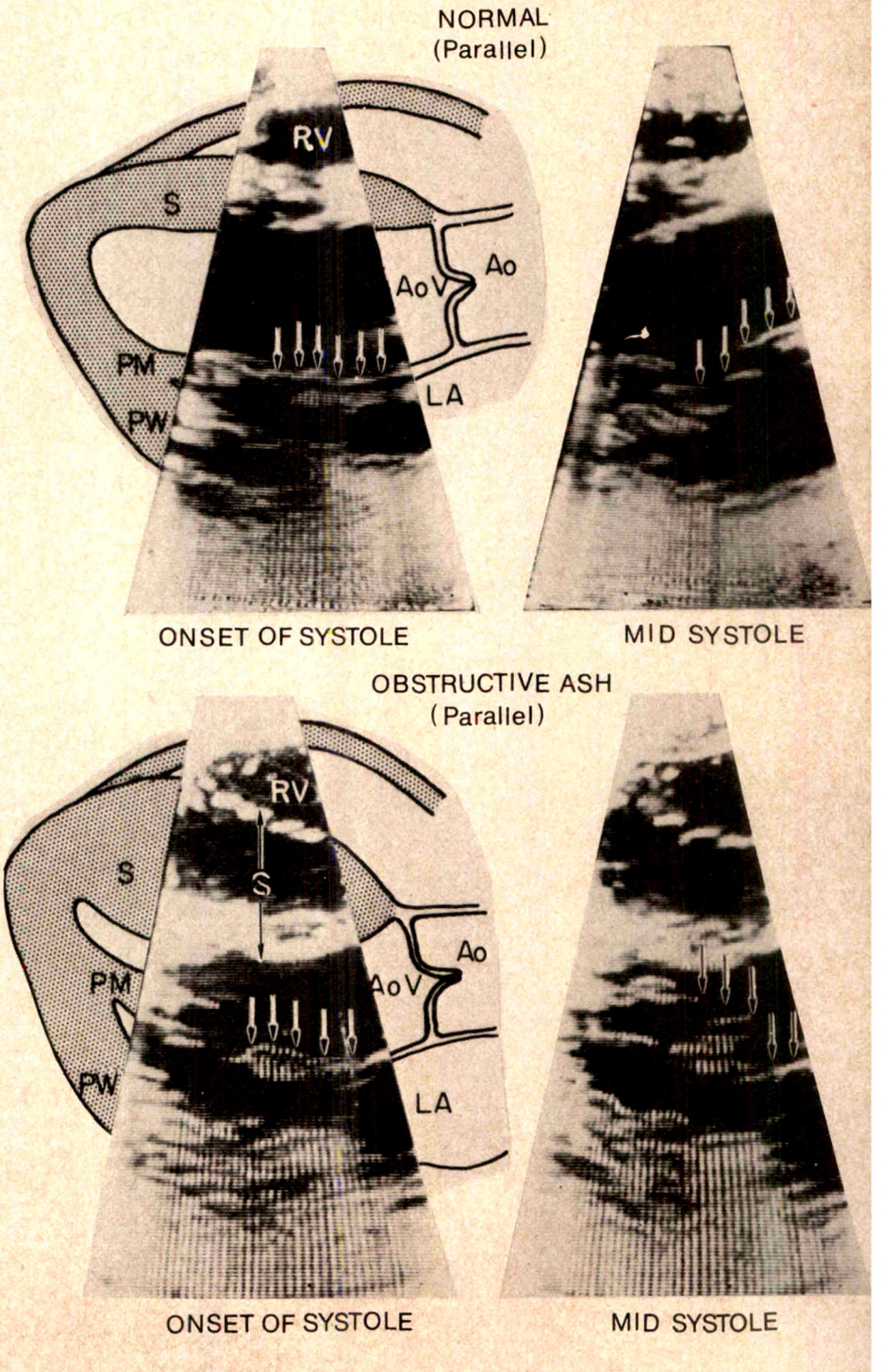

FIGURE 5. Unretouched stop-frame two-dimensional echocardiographic images (with diagrammatic sketch for orientation) obtained with the sector scanner oriented parallel to the long axis of the left ventricle in a normal subject **(top)** and a patient with obstructive asymmetric septal hypertrophy (ASH) **(bottom). Left panels** obtained at onset of systole, **right panels** in mid-systole. In obstructive asymmetric septal hypertrophy, the anterior mitral leaflet **(outlined by the arrows)** is seen to move toward the ventricular septum in mid-systole by bending at a right angle to both the proximal portion of the anterior mitral leaflet and the papillary muscles **(lower right).** The portion of ventricular septum adjacent to the right ventricle is relatively echo-free, a finding confirmed by one-dimensional echocardiographic study and by biventricular angiography. Ao = aorta; AoV = aortic valve; LA = left atrium; PM = papillary muscles; PW = posterior left ventricular wall; RV = right ventricle; S = ventricular septum.

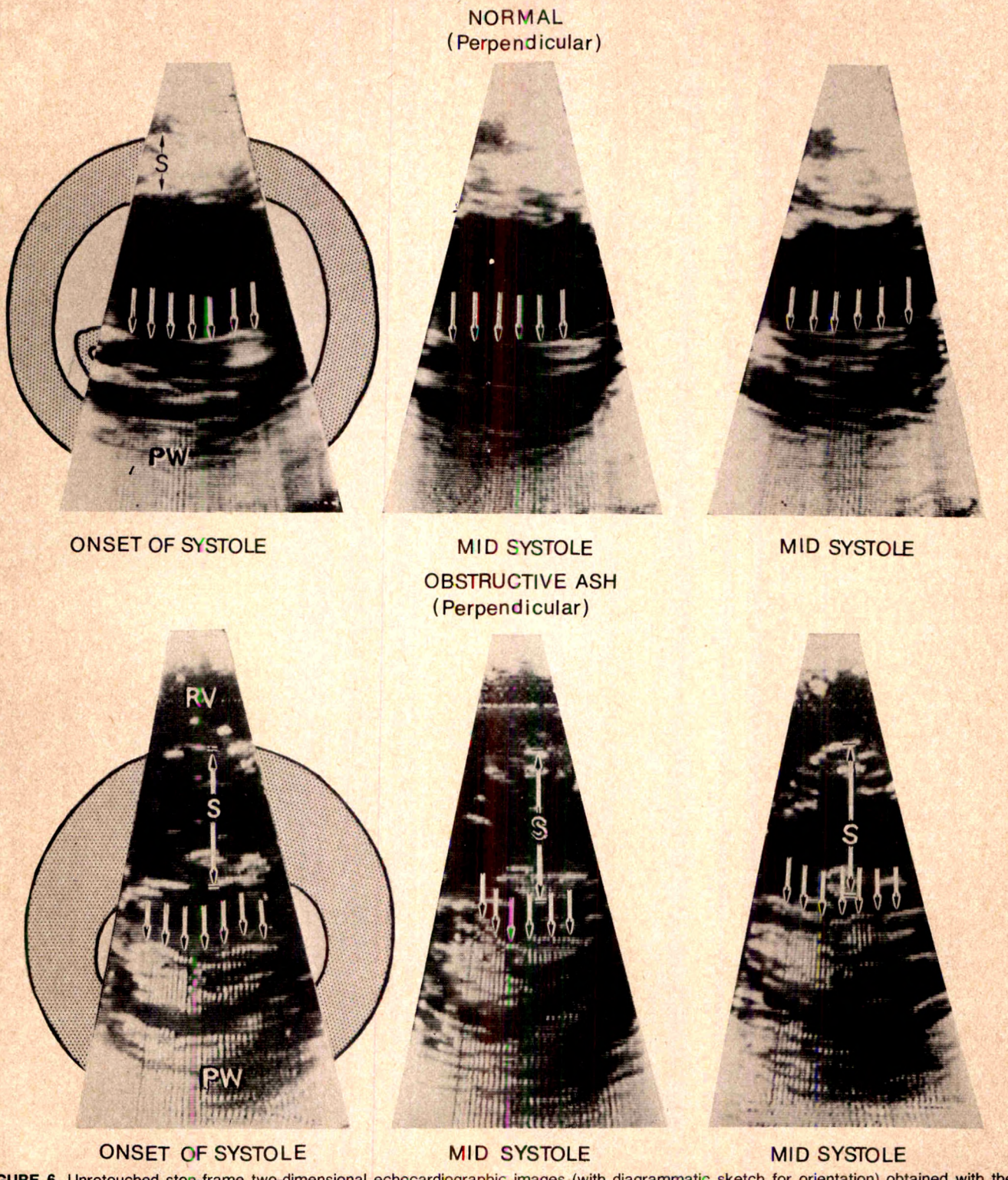

FIGURE 6. Unretouched stop-frame two-dimensional echocardiographic images (with diagrammatic sketch for orientation) obtained with the sector scanner oriented perpendicular to the long axis of the left ventricle at the level of the tip of the mitral valve in the same normal subject **(top)** and the same patient with obstructive asymmetric septal hypertrophy (ASH) **(bottom)** whose findings are shown in Figure 5. **Left panels,** obtained at onset of systole, **center panels** in mid-systole, and **right panels** shortly afterward but still in mid-systole. In obstructive asymmetric septal hypertrophy, the anterior mitral leaflet **(outlined by arrows)** is seen to move forward in mid-systole. In this subject, although the medial portion of the valve moves forward first **(center panel),** the entire leaflet quickly moves forward **(right panel,** 67 msec later). Abbreviations as in Figure 5.

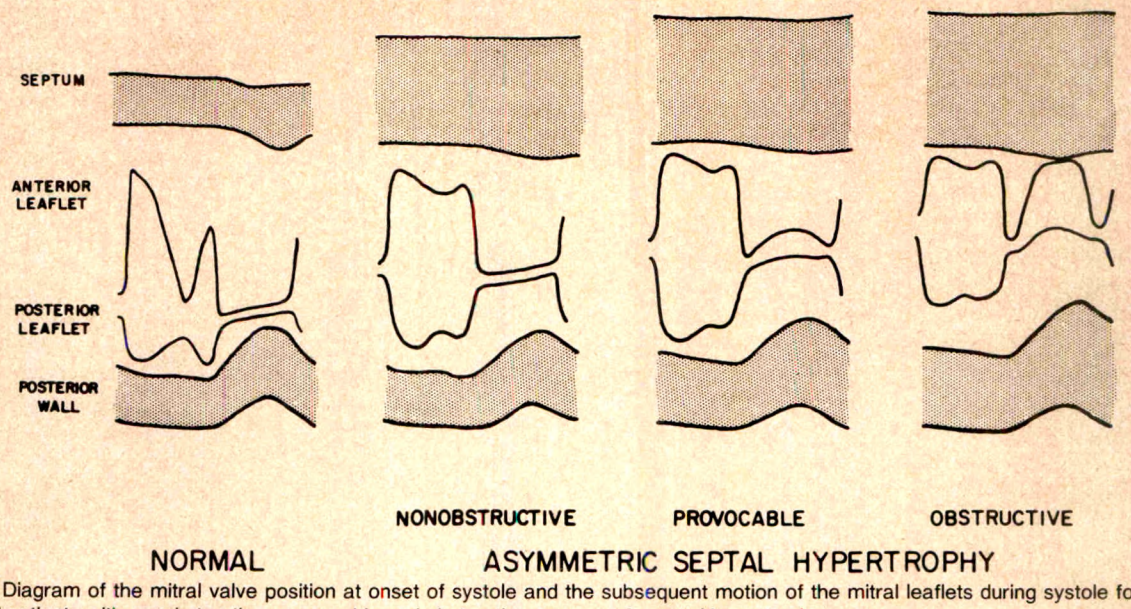

FIGURE 7. Diagram of the mitral valve position at onset of systole and the subsequent motion of the mitral leaflets during systole for a normal subject and patients with nonobstructive, provocable and obstructive asymmetric septal hypertrophy.

transverse dimension in the obstructive cases was significantly less than in the nonobstructive cases ($P < 0.01$).

Two-Dimensional Echocardiography

Parallel to left ventricular long axis: Figure 5 consists of stop-frame images from a normal subject and a patient with obstructive asymmetric septal hypertrophy. In the normal subject the anterior leaflet of the mitral valve does not bend forward toward the ventricular septum during mid-systole (upper right panel). The images from the patient with obstructive asymmetric septal hypertrophy illustrate the major abnormalities that were seen in all 11 patients with this form of the disease. Specifically, these images reveal that compared with findings in the normal subject (1) the ventricular septum is thickened markedly and has a triangular configuration as it narrows near its junction with the anterior wall of the aorta[23]; (2) the body and the tips of the papillary muscles are closer to the ventricular septum; (3) the tip of the mitral valve is anteriorly positioned in the ventricular cavity at onset of systole; and (4) the tip of the anterior mitral leaflet moves forward during mid-systole into close proximity with the ventricular septum (lower right panel). This forward motion occurs only at the tip of the mitral leaflet (that is, the tip is at a right angle to the proximal portion of the anterior mitral leaflet and to the long axis of the papillary muscles). Moreover, these images demonstrate that the papillary muscles do not pull the mitral leaflets forward by bending around the ventricular septum during systole.

Perpendicular to left ventricular long axis: Figure 6 consists of another set of stop-frame images from a normal subject and a patient with obstructive asymmetric septal hypertrophy. In the normal subject, the mitral valve at the onset of systole is positioned close to the posterior wall and well away from the ventricular septum. Throughout systole, the valve maintains this same position relative to the ventricular walls and specifically does not move forward into apposition with the ventricular septum in mid-systole (upper center and upper right panels). In the patient with obstructive asymmetric septal hypertrophy, the anterior mitral leaflet moves forward in mid-systole to contact the ventricular septum. Of note in this example, the medial portion of the mitral valve moves forward (lower center panel) before the lateral portion. Two frames later (67 msec), the entire anterior mitral leaflet has moved forward into apposition with the ventricular septum (lower right panel). In 3 of the 11 patients with obstructive asymmetric septal hypertrophy studied by two-dimensional echocardiography, the lateral portion of the mitral valve moved forward first, whereas in 2, the initial movement occurred at the medial portion of the valve; in 6, neither side could be seen to move first.

Discussion

Factors Causing Left Ventricular Outflow Obstruction

Abnormal forward motion of anterior mitral leaflet during systole: The outflow obstruction that occurs in some patients with asymmetric septal hypertrophy (that is, those with classic idiopathic hypertrophic subaortic stenosis) is caused by narrowing of the left ventricular outflow tract during systole by the forward movement of the anterior leaflet of the mitral valve, resulting in its apposition with the greatly hypertrophied ventricular septum. The observations presented in this study (depicted diagrammatically in Fig. 7) provide insight into how this occurs. In normal subjects, the mitral valve at onset of systole is positioned well away from the septum and close to the posterobasal left ventricular free wall. In asymmetric septal hypertrophy, the mean septal-mitral valve distance progressively decreases from nonobstructive to provocable and obstructive disease, whereas the average mitral valve-posterior wall dis-

tance increases progressively. Moreover, the abnormal forward motion of the anterior mitral leaflet during systole is absent in nonobstructive, minimal to moderate in provocable and prominent in obstructive disease. This diagram summarizes the one-dimensional echocardiographic data and illustrates that the degree of narrowing of the left ventricular outflow tract *at the onset of systole* appears to be an important factor in determining whether the anterior leaflet moves abnormally forward later in systole, thereby causing obstruction to left ventricular outflow.

Decrease in left ventricular transverse dimension: The decreased septal-mitral valve distance observed in obstructive asymmetric septal hypertrophy could occur if the total ventricular transverse dimension at the level of the tip of the mitral valve were reduced in these patients compared with the dimension in normal subjects (and those with nonobstructive asymmetric septal hypertrophy). Although this was, in fact, the case, the mean difference between the transverse dimension of normal subjects and patients with obstructive asymmetric septal hypertrophy was only 5 mm, a distance considerably less than the 15 mm difference between the septal-mitral valve distance in these two groups. Therefore, a decrease in left ventricular transverse dimension (as might be expected because of the marked septal hypertrophy[12,28]) cannot entirely explain the proximity of the mitral valve and septum at onset of systole in patients with obstructive asymmetric septal hypertrophy. Moreover, the observation that the mitral valve-posterior wall distance is increased (20.0 mm in obstructive disease versus 9.8 mm in normal subjects) and the septal-mitral valve distance is decreased indicates that, at the onset of systole, the mitral valve is actually displaced forward relative to the left ventricular cavity. The mechanisms responsible for this forward positioning at onset of systole are unclear but may be related either to tethering of the mitral valve by abnormally positioned papillary muscles[5,6,12,24,25] or to distortion of the left ventricle caused by the extreme hypertrophy of the ventricular septum, or to both.

Factors Causing Abnormal Forward Motion of Anterior Mitral Leaflet

That the degree of narrowing of the left ventricular outflow tract at onset of systole is not the only factor determining whether outflow obstruction develops is indicated by the overlapping values of septal-mitral valve distance in patients with asymmetric septal hypertrophy with and without outflow obstruction. Thus, an additional factor or factors must be invoked to explain the abnormal forward motion of the anterior mitral leaflet that occurs in systole. When one considers the various factors that could conceivably cause the mitral leaflets to move forward, it appears that three different mechanisms might be involved. For example: (1) The mitral valve leaflets could be pulled against the septum by contraction of papillary muscles that are bent around a bulging ventricular septum during systole (as suggested by angiographic and necropsy studies[5,6,12,24,25]); (2) the mitral valve leaflets could be sucked forward by a high velocity stream of blood that is ejected through an already narrowed outflow tract (that is, a Venturi effect[26]); and (3) the mitral valve leaflets could be pushed forward from behind because they are abnormally positioned across the outflow stream.

Shortening of papillary muscles along long axis: The two-dimensional echocardiographic images from patients with obstructive asymmetric septal hypertrophy presented in this study appear to rule out the first mechanism as the cause of the outflow obstruction in most patients. These images revealed that only the tip of the anterior mitral leaflet moves forward to contact the ventricular septum during systole; that is, the tip bends at a right angle to both the proximal portion of the anterior mitral leaflet and the long axis of the papillary muscles (the latter observation being particularly important in regard to the mechanism of obstruction). In addition, it is clear from these images that although the distance from the tip of the papillary muscles to the ventricular septum is smaller in patients with obstructive asymmetric septal hypertrophy than in normal subjects (as suggested by the angiographic and necropsy studies), the papillary muscles are parallel to the left side of the ventricular septum and do not bend around the ventricular septum during systole. Thus, shortening of the papillary muscles along their long axis does not appear able to produce the right angle bend of the mitral valve tip seen in the two-dimensional images. Therefore, it appears that the mitral leaflets either are sucked forward by a Venturi effect or pushed forward from behind by the stream of blood being ejected.

Hydrodynamic forces generated by left ventricle: From theoretical considerations, certain resistances (valve mass, tension of chordae tendineae, for example) must be overcome by the hydrodynamic forces (Bernoulli forces or pushing forces, or both) before the mitral leaflets will move forward. Also, the degree to which these hydrodynamic forces exceed the resistance of the valve apparatus should determine the extent of systolic anterior motion, and hence the degree of obstruction. In this regard, the observation that one side of the valve may move forward before the other side means that either the hydrodynamic forces or the resistance of the valve apparatus, or both, is not distributed uniformly across the valve. This observation also illustrates the importance of scanning across the tip of the valve when using one-dimensional echocardiographic methods to evaluate the severity of obstruction.

As a result of this investigation and our prior studies of the distribution of the myopathy in asymmetric septal hypertrophy,[27,28] we propose that left ventricular outflow obstruction occurs in patients with asymmetric septal hypertrophy as a result of the interaction of two factors: (1) narrowing of the left ventricular outflow tract at onset of systole, and (2) hydrodynamic forces generated by contraction of the left ventricle. In symptomatic patients with nonob-

structive asymmetric septal hypertrophy, the position of the mitral valve generally is less forward than in those with obstructive disease; and both the septum and the left ventricular free wall are extensively involved by the myocardial defect[27,28] (presumably resulting in a decrease in hydrodynamic forces during left ventricular contraction). Either of these factors could prevent outflow obstruction from occurring. In contrast, the outflow tract of patients with obstructive asymmetric septal hypertrophy is narrowed at the onset of systole and the septum, but not the free wall, is involved by the myocardial defect[27,28] (the lack of free wall involvement presumably resulting in normal or near normal contractile function). These factors should combine to produce outflow obstruction. In patients with provocable asymmetric septal hypertrophy, we suggest that the two factors are closely counterbalanced, resulting in no obstruction under basal conditions but significant gradients when interventions tip the balance in favor of obstruction.

Clinical implications: If this hypothesis of the mechanism of left ventricular obstruction in asymmetric septal hypertrophy is correct, then interventions that alter the degree of outflow obstruction presumably would do so by altering (1) septal-mitral valve distance at the onset of systole, (2) hydrodynamic forces generated by contraction of the left ventricle, or (3) both. In this regard, relief of the outflow obstruction (and abnormal anterior systolic mitral valve motion) that occurs after septal myotomy-myectomy may be largely explained by the creation of an enlarged outflow tract that reduces outflow tract blood flow velocity and hence decreases the hydrodynamic forces acting on the mitral leaflets. Thus, by combining the results of this study with those of our previous studies on the distribution of the myopathy in asymmetric septal hypertrophy, it has been possible to construct a hypothesis that may explain why some patients with asymmetric septal hypertrophy have left ventricular outflow obstruction but others do not.

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First Heart Sound and Ejection Sounds

Echocardiographic and Phonocardiographic Correlation with Valvular Events

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To provide additional information on the relation of valvular events to the principal components of the first heart sound (S_1), combined echocardiograms and phonocardiograms were recorded in 49 subjects, chosen because of audible splitting of S_1 or a combination of S_1 and an ejection sound. The subjects included 14 normal persons, 16 patients with a variety of predominantly right-sided heart conditions, 7 with mitral stenosis, 3 with pulmonary stenosis and 9 with aortic valve disease or systemic hypertension. A precise relation was found between completion of closure of the atrioventricular (A-V) valves manifested in the echocardiogram and the high-frequency components of S_1 (M_1 and T_1). The average time from the Q wave of the electrocardiogram to M_1 was 0.06 ± 0.003 second and the Q-T_1 interval was 0.09 ± 0.002 second. In mitral stenosis the Q-M_1 interval was delayed to 0.10 ± 0.005 second, resulting in some instances in reversed splitting of S_1. In pulmonary stenosis, the ejection sound occurred 0.10 ± 0.003 second from the Q wave. In 7 of the 16 patients with various right-sided abnormalities, but without valvular stenosis, an ejection sound of pulmonary origin occurred 0.18 ± 0.012 second from the Q wave. In the nine patients with aortic valve disease or systemic hypertension, the time from the Q wave to the aortic ejection sound was 0.13 ± 0.004 second. With only two exceptions the ejection sounds of aortic and pulmonary origin coincided exactly with the achievement of a fully opened position of the respective semilunar valve. Our findings support the postulate that M_1, T_1 and the ejection sounds occur in association with closing or opening of valves with consequent sudden deceleration or acceleration of a column of blood that, in turn, results in vibrations of the cardiohemic system and audible sounds.

The origin of the first heart sound (S_1) has been the subject of debate for more than 100 years. Dock[1] attributed the genesis of the major components of S_1 to the closing of the mitral and tricuspid valves at the moment of ventricular contraction. Details of splitting of S_1 were further elucidated by the meticulous studies of Leatham.[2] He found that the mitral component (M_1) preceded the tricuspid component (T_1) by 0.02 to 0.03 second in healthy subjects. M_1 was louder at the cardiac apex or mitral area and T_1 was louder at the lower left sternal edge. The valvular theory of the genesis of S_1 was furthered by the investigations of Orias and Braun-Menendez,[3] who found a wider separation of M_1 and T_1 in bundle branch block. Reversal of the major components of S_1 was noted by Cossio and Berconsky[4] in mitral stenosis; in this condition M_1 is delayed owing to the pressure gradient between the left atrium and ventricle. The valvular theory has also been supported by the work of Braunwald and Morrow[5] and Heintzen.[6] Other investigators,[7–9] however, regard the rise of left ventricular pressure, manifested by its first derivative (dP/dt), and ejection of blood into the aorta as the principal factors in the production

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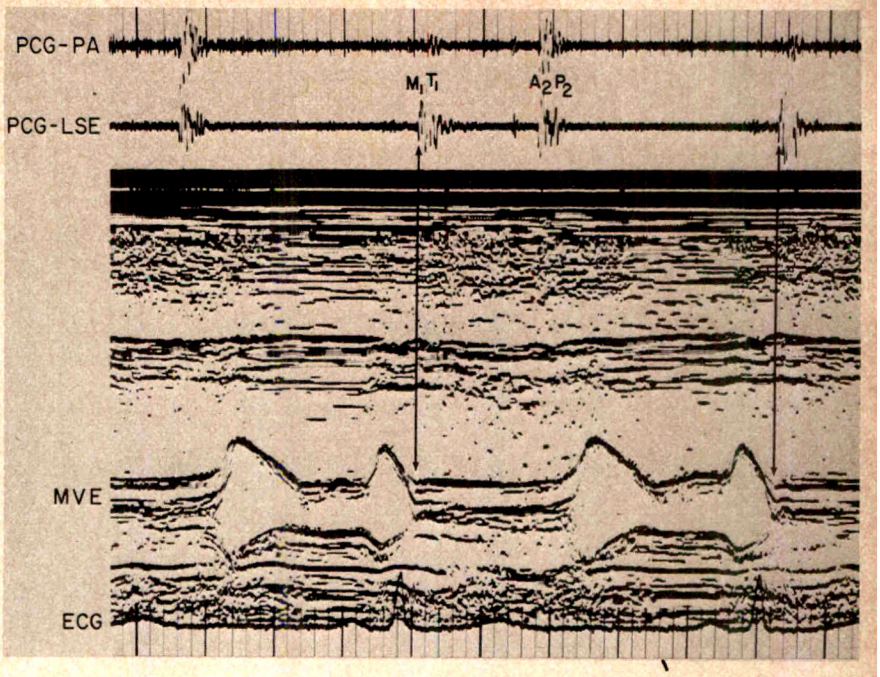


FIGURE 1. Group I. Echo-phonocardiogram of a normal subject. Phonocardiograms from pulmonary area (PCG-PA) and left sternal edge (PCG-LSE) are shown at **top.** The mitral valve echo (MVE) demonstrates both leaflets opening in early diastole and reopening with atrial systole. A closing movement then occurs in late diastole with the C point **(arrow)** signifying full closure of the valve with the onset of ventricular contraction. The coincidence of the C point and the beginning of the high-frequency vibrations of the first heart sound (M_1) is evident. A_2, P_2 indicate the major components of the second heart sound. Time lines 0.04 second.

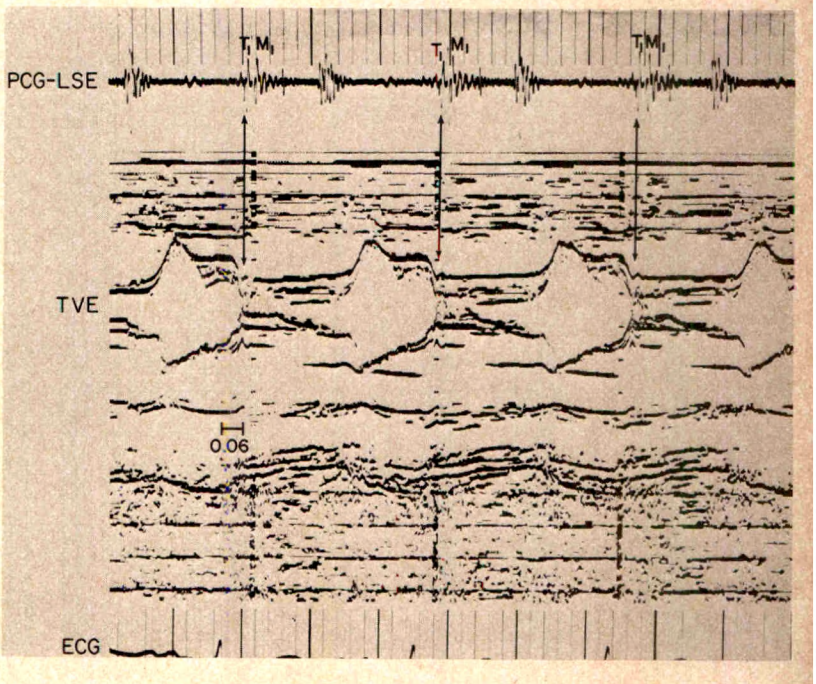


FIGURE 2. Group III, Case 7. Echo-phonocardiogram from a young man with severe mitral stenosis. Echoes from the tricuspid valve (TVE) show two of the three leaflets. Movements are similar to those of the mitral valve (MVE) in Figure 1. In this case, however, the C point indicating full closure of the tricuspid valve occurs 0.06 second after the Q wave of the electrocardiogram which is prior to the analogous point on the MVE. The **arrow** indicates the close coincidence of the tricuspid C point with the first high-frequency vibrations of the first heart sound which are therefore designated T_1. M_1 (shown in Figure 9) is coincident with the C point on the MVE and 0.02 second later, indicating reversed splitting of S_1.

of S_1. Luisada et al.[10,11] emphasized the exclusively left-sided origin of S_1 in canine experiments that demonstrated an absence of sound production by the tricuspid valve.

Ejection sounds of pulmonary and aortic origin may contribute to the constellation of sounds at the onset of systole. At times it is difficult to differentiate these from other components comprising S_1. The origin of ejection sounds is believed to be valvular in the case of semilunar valve stenosis[12,13] and vascular in hypertension of the pulmonary artery or aorta.[14]

The demonstration in recent years that movements of all four heart valves can be traced in strip chart echocardiograms in conjunction with phonocardiograms and other graphic tracings suggested that this method might provide new information on the various factors contributing to the first heart sound. We therefore chose for study patients who had multiple components of S_1, or S_1 plus an ejection sound, and investigated the temporal relation of these vibrations to atrioventricular (A-V) valve closure and semilunar valve opening. Since the echoes from the tricuspid valve are more easily obtained in conditions

TABLE I

Timing of Heart Sounds

Case no.	Diagnosis	Age (yr)	Q–M_1 (sec)	Q–T_1 (sec)	Q–Pulmonary Ejection Sound (sec)	QRS Duration (sec)
		Group I (14 Normal Subjects)				
Mean ± SEM		28.2 ± 5.1	0.06 ± 0.003	0.09 ± 0.002	...	0.07 ± 0.003
		Group II (Right-Sided Abnormalities)				
1	RBBB	29	0.08	0.14	...	0.12
2	RBBB	34	0.06	0.13	...	0.12
3	RBBB	20	0.06	0.10	...	0.12
4	ASD; RBBB	63	0.09	0.14	0.24	0.155
5	RBBB	59	0.08	0.14	...	0.12
6	ASD; pulmonary hypertension	55	0.06	0.12	0.15	0.12
7	ASD; pulmonary hypertension	17	0.07	0.12	...	0.12
8	ASD with repair	19	...	...	0.20	0.15
9	ASD with repair	38	0.06	0.08	0.15	0.05
10	ASD with repair	27	0.08	0.13	0.18	0.10
11	ASD with repair	32	0.08	0.12	...	0.10
12	Eisenmenger syndrome	33	0.07	0.08	0.16	0.08
13	Eisenmenger syndrome	19	0.07	0.09	0.16	0.07
14	Cor pulmonale; pulmonary hypertension	48	0.09	0.15	...	0.12
15	Pulmonary hypertension; TR	46	0.06	0.09	...	0.07
16	Ebstein's anomaly	20	0.09	0.15	...	0.11
Mean ± SEM		34.9 ± 3.7	0.07 ± 0.003	0.12 ± 0.006	0.18 ± 0.012	0.10 ± 0.007

associated with dilatation of the right ventricle, the patients in the series are predominantly those with right-sided cardiac abnormalities.

Materials and Methods

Forty-nine patients, ranging in age from 8 to 63 years, with splitting of the first heart sound or an audible ejection sound were divided into five groups (Table I):

Group I: 14 patients with splitting of S_1 but no evidence of heart disease by history, physical examination, chest X-ray examination and electrocardiogram.

Group II: 16 patients with either right bundle branch block, cor pulmonale, atrial septal defect, Ebstein's anomaly, Eisenmenger's syndrome or other right-sided abnormalities.

Group III: 7 patients with mitral stenosis.

Group IV: 3 patients with pulmonary valve stenosis.

Group V: 9 patients with aortic ejection sounds associated with aortic stenosis or regurgitation or systemic hypertension.

Combination echocardiograms and phonocardiograms were recorded on a six channel Cambridge multichannel physiologic recorder on photographic paper at a paper speed of 100 mm/sec in a sound-conditioned room. Echocardiograms were obtained by means of a Smith-Kline Ekoline 20 ultrasonoscope with a 2.25 megahertz transducer of 0.5 inch diameter. The output of the ultrasonoscope was displayed on the oscilloscope of the multichannel recorder in conjunction with an electrocardiogram and phonocardiograms from the principal valvular areas. These included the second interspace to the left and right of the sternum, the left sternal edge in the fourth interspace, and the apex or "mitral" area. Cambridge Leatham microphones were used for sensing heart sounds.* Patients were studied in the supine position. Echoes from the various heart valves were obtained by the techniques described by Feigenbaum.[15] Complete closure of the mitral and tricuspid valves was assumed at the point where anterior and posterior leaflets meet near the onset of ventricular systole (Fig. 1 and 2). This point coincided with a sharp shoulder on the echo of the anterior leaflet of both A-V valves.

*The microphone has a constant output in the range of 100 to 300 cycles/sec and increases in sensitivity by 30 decibels up to 1,500 cycles/sec. The phonocardiographic amplifier setting at the medium-frequency range used in this study has a linear response of 250 to 1,000 cycles/sec. From 250 to 100 cycles/sec there is a decrease of 20 decibels.

TABLE I (*Continued*)

Case no.	Diagnosis	Age (yr)	Q–M_1 (sec)	Q–T_1 (sec)	Q–Pulmonary Ejection Sound (sec)	QRS Duration (sec)
			Group III (Mitral Stenosis)			
1		29	0.10	0.08	...	0.07
2		31	0.09	0.07	...	0.08
3		55	0.10	0.11	...	0.08
4		34	0.10	0.09	...	0.07
5		53	0.10	0.10	...	0.08
6		13	0.08	0.07	...	0.06
7		28	0.12	0.09	...	0.10
Mean		34.7	0.10	0.09	...	0.08
± SEM		± 5.6	± 0.005	± 0.005		± 0.007
			Group IV (Pulmonary Valve Stenosis)			
1		13	0.06	0.08	0.10	0.08
2		11	0.06	0.08	0.11	0.08
3		8	0.06	0.09	0.11	0.08
Mean		10.6	0.06	0.08	0.11	0.08
± SEM		± 1.1		± 0.003	± 0.003	
			Group V (Aortic Stenosis, Aortic Regurgitation and Systemic Hypertension)			
1	AS	21	0.07	0.09	0.14*	0.08
2	Bicuspid valve	47	0.05	...	0.11	0.09
3	AS	18	0.06	0.10	0.14	0.07
4	AS	8	0.06	...	0.12	0.08
5	AS	20	0.07	...	0.13	0.08
6	AS	20	0.06	0.08	0.12	0.08
7	AR	43	0.06	0.09	0.15	0.08
8	AR	20	0.06	0.09	0.13	0.08
9	Systemic hypertension	35	0.06	0.08	0.13	0.08
Mean		25.7	0.06	0.09	0.13	0.08
± SEM		± 4.3	± 0.002	± 0.003	± 0.004	± 0.007

* Data in this column for Group V refer to Q–aortic ejection sound (sec).

AR = aortic regurgitation; AS = aortic stenosis; ASD = atrial septal defect; RBBB = right bundle branch block; SEM = standard error of the mean; TR = tricuspid regurgitation.

Therefore in instances when it was not possible to record both leaflets, this sharp shoulder was assumed to be the C point, signifying completion of closure. The maximal posterior excursion of the posterior leaflet of the pulmonary valve was regarded as indicative of peak opening of this semilunar valve (Fig. 3). The transmission time for sonic and ultrasonic vibrations from source to recording on photographic paper is negligible. Therefore the relation of valvular to acoustical events was demonstrated by the construction of vertical lines at the points of completion of valvular movements as defined. The time of occurrence of the several elements of the complex of heart sounds was taken to be the initial high-frequency vibrations, as is customary in phonocardiographic interpretation.[16]

Results

Group I (splitting of first heart sound): In these 14 patients with no known heart disease, mitral valve closure preceded tricuspid valve closure by 0.03 second (Table I). The C point or complete closure of the mitral valve coincided precisely with the onset of the first group of high-frequency vibrations in S_1 (Fig. 1 and 4A), and the corresponding point on the tricuspid valve echo had a similar relation to the second group of high-frequency vibrations (Fig. 4B). The first of these two elements of S_1 is designated M_1 and the second T_1. M_1 was most intense at the apex or mitral area and T_1 at the lower left sternal edge. The time intervals from the Q wave of the electrocardiogram to the C point on the mitral and tricuspid echoes and the respective sounds, M_1 and T_1, are indicated in Table I.

Group II (patients with right bundle branch block, cor pulmonale, atrial septal defect or other right-sided abnormalities): These patients had a longer than normal interval between completion of closure of the mitral and tricuspid valves (Table I). A similar exaggerated interval was noted between M_1 and T_1, these sounds again coinciding almost exactly with completion of closure of the corresponding A-V valve (Fig. 5 to 7). The greatest separation of the elements of S_1 was found in the patient with Ebstein's anomaly (Group II, Case 16). In this patient two leaflets of each of the A-V valves could be visualized simultaneously in the echo-phonocardiogram (Fig. 7). The excursion of the tricuspid valve

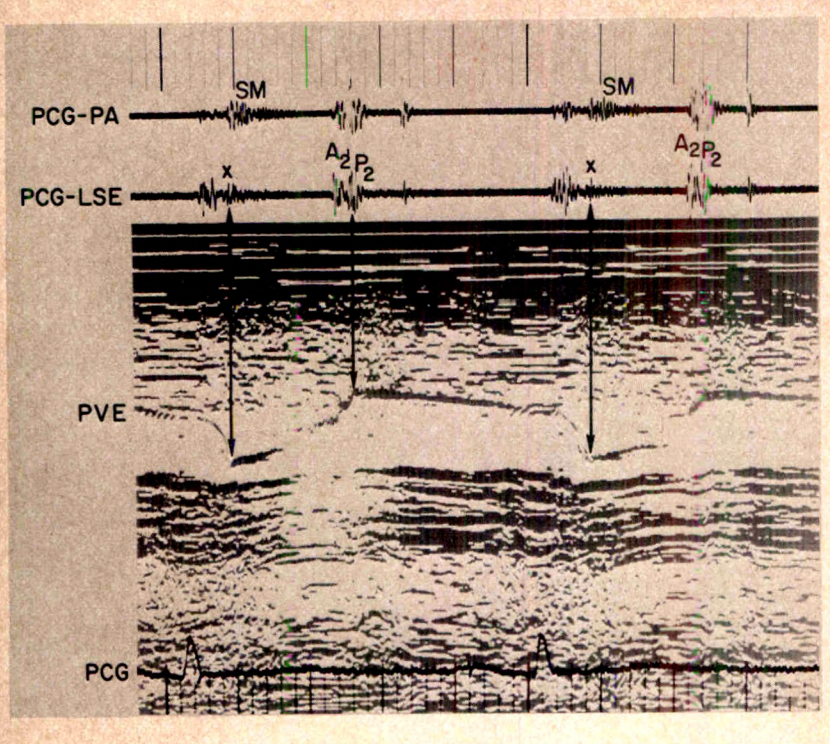
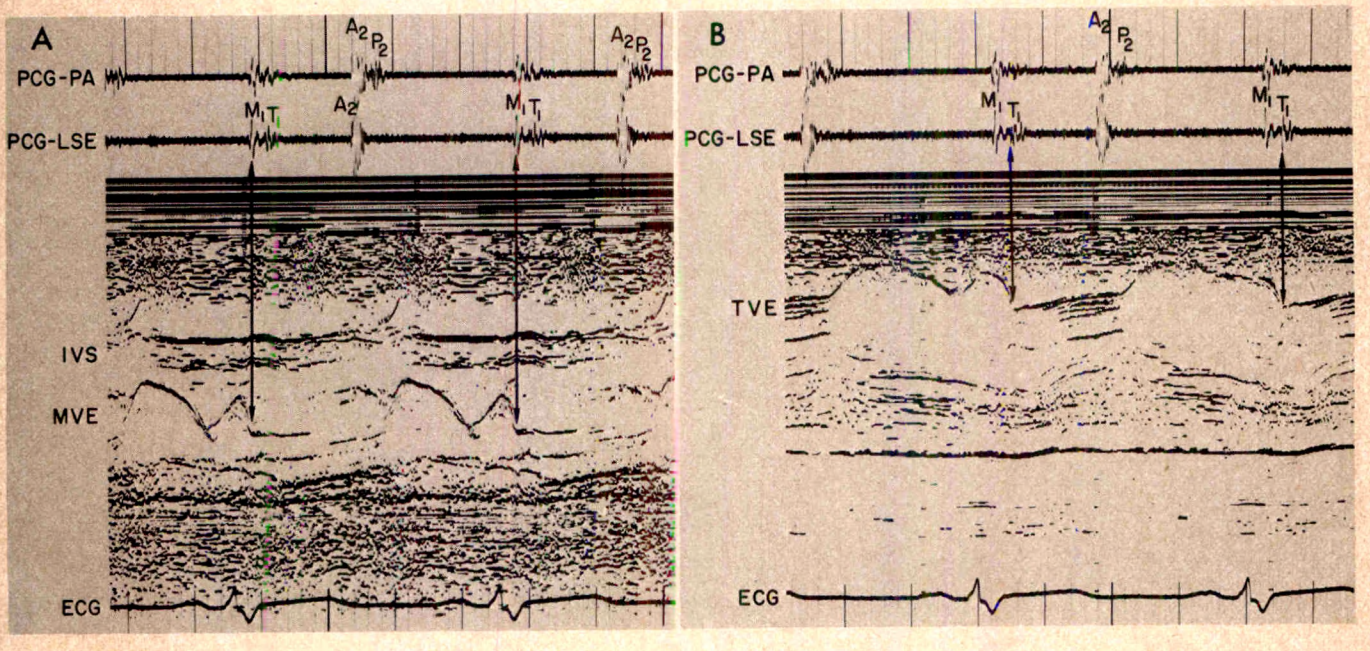


FIGURE 3 (left). Group II, Case 9. Echo-phonocardiogram from a woman after closure of an atrial septal defect. Phonocardiograms show an ejection sound (x) as well as wide, but variable, splitting of the second heart sound. There is a slight systolic murmur (SM). Echoes from the pulmonary valve (PVE) demonstrate a downward or opening movement of the posterior cusp. This reaches its full excursion at precisely the time of the ejection sound. Closure of the valve (upward movement) culminates at the time of P_2.

FIGURE 4 (bottom). Group II, Case 1. Echo-phonocardiogram from a young woman whose heart was normal except for right bundle branch block. **A,** the C point of the mitral valve echo (MVE) occurs at the time of M_1. **B,** the C point of the tricuspid valve echo (TVE) is coincident with T_1. IVS = interventricular septum.



was abnormally large and the completion of closure was significantly delayed. The C point on the echo of the tricuspid valve corresponded exactly with the loud "sail sound" or delayed T_1 that is characteristic of this condition.[17,18] The mitral valve moved through a much smaller amplitude and closed on time but with a barely preceptible M_1.

Seven of the patients in Group II had pulmonary ejection sounds associated with hypertension or dilatation of the pulmonary artery. The timing of the sound was delayed with respect to M_1 and T_1, occurring 0.15 to 0.24 second after the Q wave. Nevertheless in all but one instance the ejection sound was precisely synchronous with achievement of a fully open position by the pulmonary valve cusps (Fig. 8). The exception was Patient 12 in Group II, who had deep cyanosis due to a ventricular septal defect of the Eisenmenger type. His ejection sound occurred 0.02 second after full opening of the valve. The significance of this relation will be discussed later.

Group III (mitral stenosis): The tracings in these patients demonstrated the characteristic delayed downslope of the mitral valve echo in diastole. This plateau was abruptly terminated by a brisk closure movement at the onset of ventricular systole (Fig. 9). Closure of the mitral valve was associated with a loud

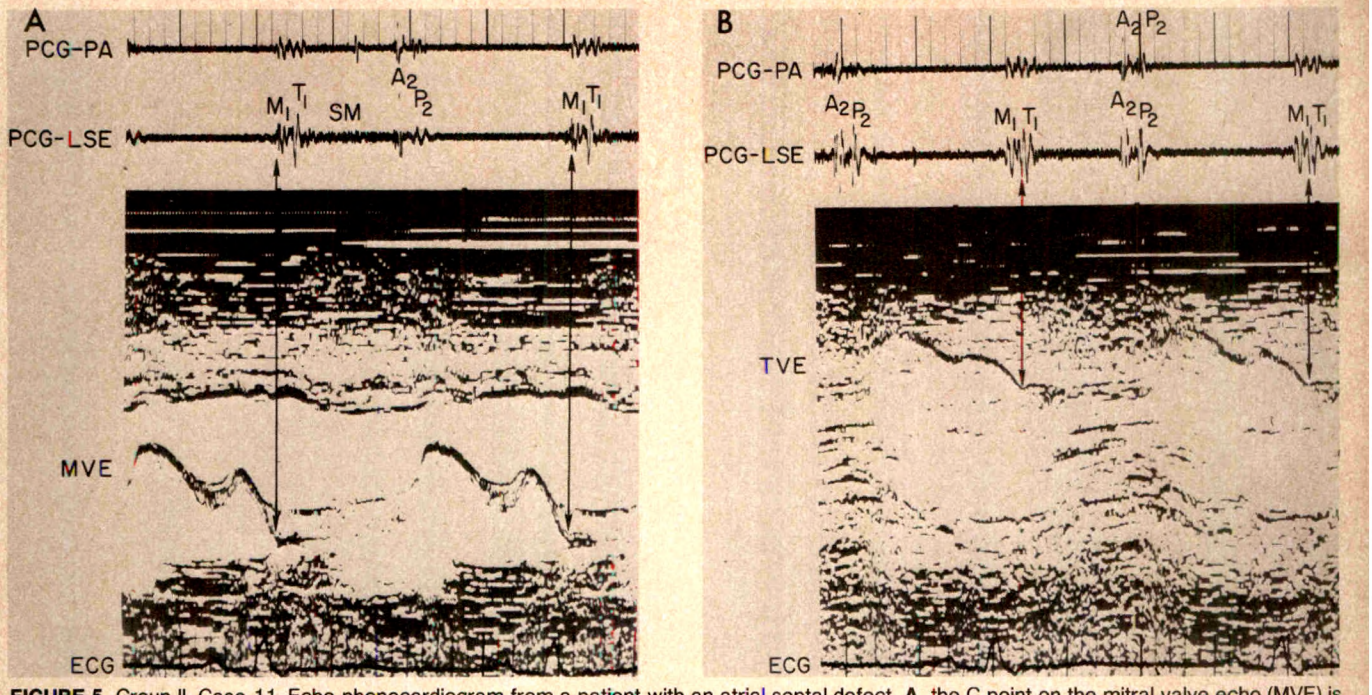


FIGURE 5. Group II, Case 11. Echo-phonocardiogram from a patient with an atrial septal defect. **A,** the C point on the mitral valve echo (MVE) is precisely synchronous with the onset of the high-frequency vibrations of the first heart sound (M_1). A soft systolic murmur (SM) is also illustrated. **B,** the C point of the anterior leaflet of the tricuspid valve (TVE) is coincident with the second group of high-frequency vibrations of S_1, designated T_1.

M_1. A separate group of high-frequency vibrations could be identified at the left sternal edge, coincident with the C point of the tricuspid valve echo. In the five most severe cases, a delay in mitral valve closure, resulting from a large pressure gradient between the left atrium and ventricle, led to a reversed splitting of S_1, with M_1 occurring after T_1 (Table I).[19]

Group IV (pulmonary valve stenosis): In these three patients an ejection sound recorded in early systole coincided with peak opening of the pulmonary valve. Completion of valvular opening and the accompanying high-frequency ejection sound occurred 0.10 to 0.11 second after the Q wave, permitting a separation from M_1 and T_1. These sounds occurred earlier and, as in the other groups, were coincident with closure of the respective atrioventricular valves.

Group V (ejection sounds of aortic origin): Six of these nine patients had aortic valve stenosis, two had aortic regurgitation and one had systemic hypertension. The ejection sound was heard and recorded widely over the precordium and it occurred 0.11 to 0.15 second from the onset of the Q wave. In all but one instance, the ejection sound and the achievement of full opening of the aortic cusps were precisely coincident (Fig. 10). The exception was Patient 7 (aortic regurgitation), whose valvular opening occurred 0.13 second after the Q wave and whose ejection sound appeared 0.02 second later.

Discussion

Genesis of First Heart Sound

First component of S_1 (M_1): Our findings are in agreement with those of previous investigators[1–6]

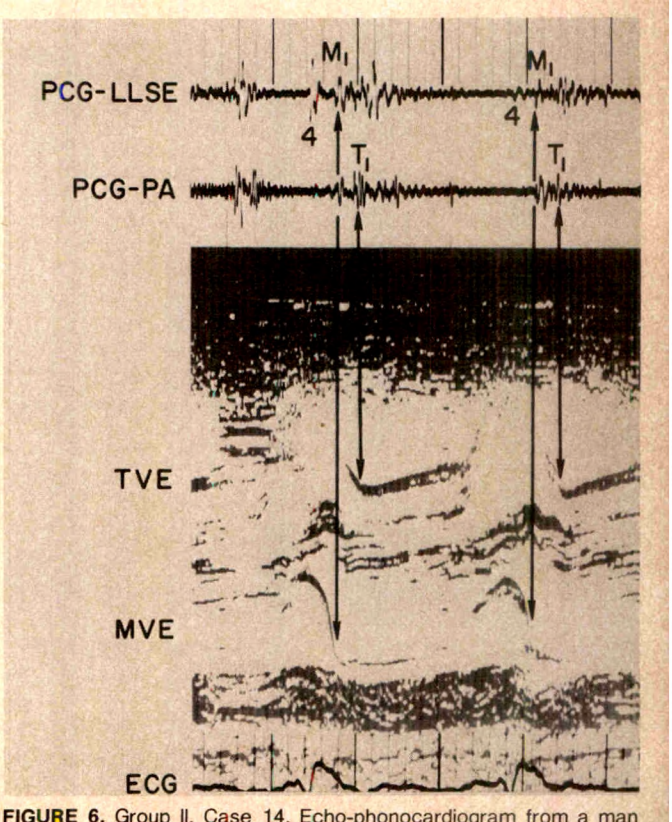


FIGURE 6. Group II, Case 14. Echo-phonocardiogram from a man with cor pulmonale. Echoes from both A-V valves are illustrated. The complex of sounds consists of a fourth sound or atrial gallop (4) best seen in the phonocardiogram from the lower left sternal edge (PCG LLSE). The C point of the mitral valve echo (MVE) is coincident with M_1 and the C point of the tricuspid valve echo (TVE) with T_1. There is also a systolic murmur in the phonocardiogram from the lower left sternal edge.

who have emphasized the importance of valvular events in the genesis of the principal high-frequency vibrations of the first heart sound. Di Bartolo et al.,[7] however, excluded mitral valve closure as a contributing factor in the genesis of S_1 because the first major high-frequency component of this sound followed the crossover of pressures between the ventricle and atrium by 23 msec in canine experiments. These investigators therefore preferred to attribute S_1 to the abrupt increase in pressure in the left ventricle during the isovolumic phase of contraction. Similar conclusions were later reached by Luisada et al.[8] and Van Bogaert et al.[9] However, Faber[21] showed conclusively that mitral valve closure does not take place at zero A-V pressure gradient but about 22 msec later.

These findings have recently been confirmed in an elegant study by Laniado et al.,[22] who used synchro-

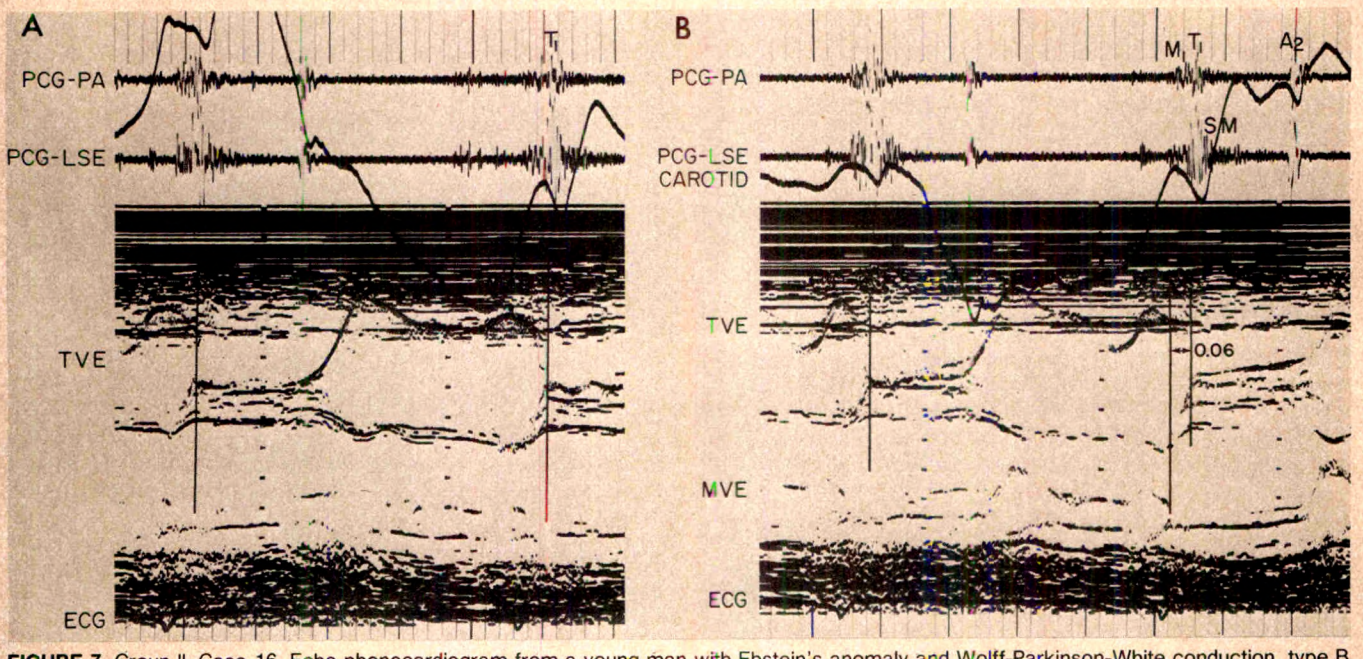


FIGURE 7. Group II, Case 16. Echo-phonocardiogram from a young man with Ebstein's anomaly and Wolff-Parkinson-White conduction, type B. **A,** two leaflets of the tricuspid valve are seen. The ballooning movements of the valve create an enormous separation in diastole. The C point is much delayed and is coincident with the loud T_1 or "sail sound." **B,** echoes from both A-V valves are seen. The excursion of the mitral valve leaflets is relatively diminutive and the C point of this valve precedes the C point of the tricuspid valve by 0.06 second.

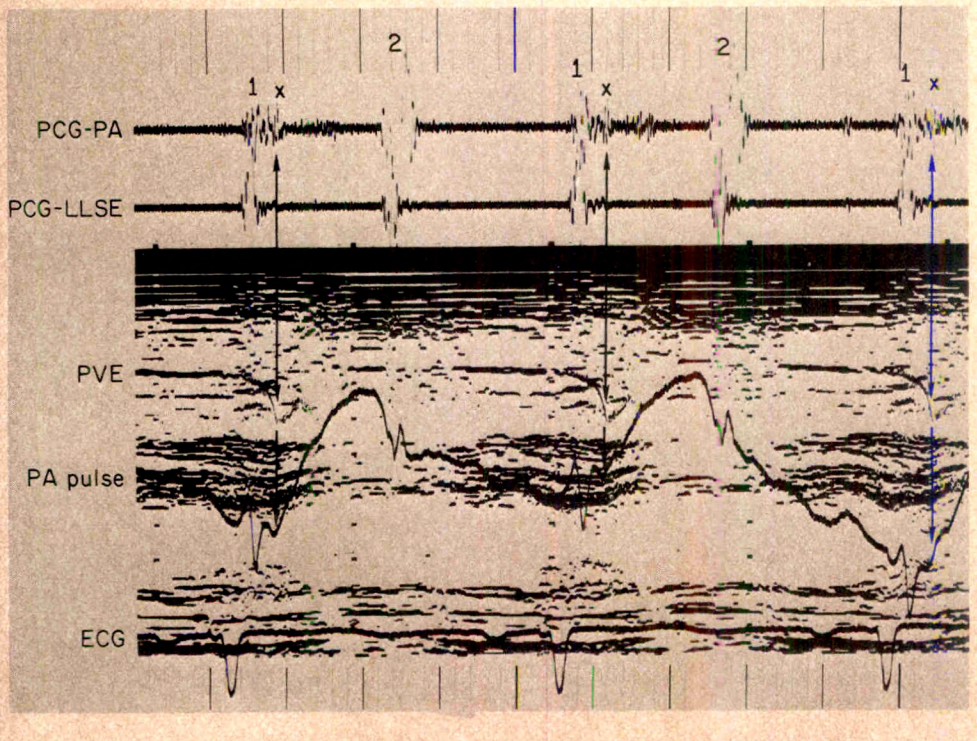


FIGURE 8. Group II, Case 13. Echo-phonocardiogram from a young woman with severe pulmonary hypertension due to a ventricular septal defect of the Eisenmenger type with cyanosis. The pulmonary ejection sound (x) is coincident with the achievement of a fully open position by the posterior cusp of the pulmonary valve (PVE). A recording of chest wall movement in the second left intercostal space parasternally (PA pulse) reflects the bulging of the pulmonary artery. The *onset* of this event coincides with valve opening and ejection sound.

nized high-fidelity pressure tracings and cinefluorograms of mitral valve motion facilitated by artificial radiopacification of the leaflets to demonstrate that the mitral valve leaflets were still in the open position at the time of zero A-V pressure gradient. The first major component of S_1 coincided with zero mitral flow, as determined by an electromagnetic flow probe, and with the simultaneous completion of closure of the mitral valve. These events followed the A-V pressure crossover by some 20 to 40 seconds, a delay occasioned by the inertia of mitral flow. S_1 did *not* show a fixed temporal relation to peak dP/dt in their study. This close relation of S_1 to valve closure is also consistent with the recent studies of Stept et al.[23] and Lakier et al.[24]

Several investigators have applied echocardiographic techniques to the problem of the genesis of heart sounds. Edler[25] noted the coincidence of the C point on the mitral valve echo and M_1. Zaky et al.[26] reported a close relation between the intensity of M_1 and the position of the mitral valve leaflets at the onset of systole in patients with various degrees of heart block. Shah et al,[27] studying patients with heart block, found that the first sound was absent when the mitral valve was closed prematurely by atrial systole. Recently Burggraf and Craige[28] found a high correlation between the amplitude of the excursion of the mitral valve leaflets and the intensity of M_1 ($r = 0.93$) in patients with complete heart block. When the mitral valve was completely closed at the onset of ventricular systole, M_1 was absent. Systolic time intervals were measured as an index of left ventricular contractility, and a poor correlation was found between duration of the preejection period and the intensity of M_1 ($r = -0.12$). These findings relating the intensity of M_1 to position of the mitral leaflets at the onset of ventricular systole are also supported by the observation that in severe aortic regurgitation the premature closure of the mitral valve in late diastole is associated with a diminished or absent S_1.[29]

A divergent view based on echocardiographic studies of the relation of mitral valve closure to the production of S_1 was recently provided by Parisi and Milton.[30] They found that the C point in the mitral valve echo *followed* M_1 by some 19 msec, and their conclusions appear to support the cited contention of Luisada et al.[8] that valve closure and sound production are unrelated.

In summary, with respect to M_1, we support the importance of mitral valve closure in the production of the sound because of the synchrony of the C point in the mitral valve echocardiogram and the first set of high-frequency vibrations of S_1. It is not, of course, the apposition of the valve leaflets but rather the tensing of the leaflets and sudden deceleration of blood resulting from this event that could lead to vibrations of the cardiohemic system and audible sound.[31]

Second component of S_1 (T_1): The origin of the second major component of the first heart sound is even more controversial. The classic explanation attributed this group of high-frequency vibrations to

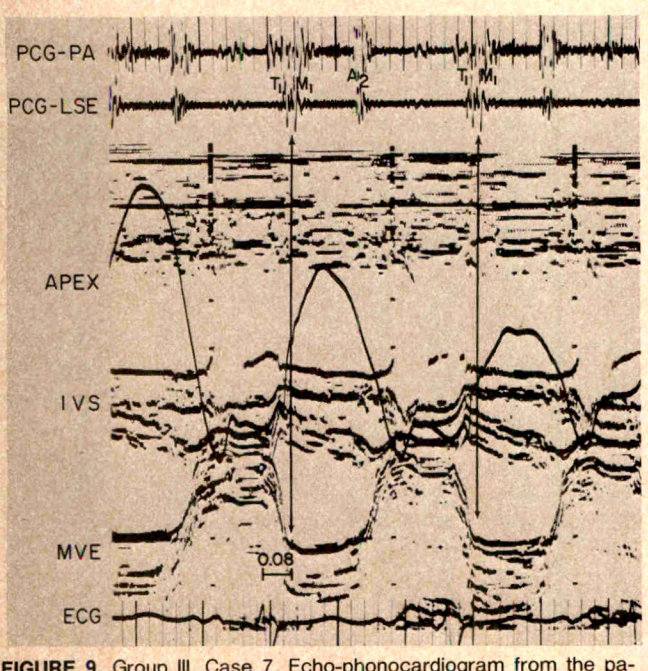


FIGURE 9. Group III, Case 7. Echo-phonocardiogram from the patient with mitral stenosis whose tracings are shown in Figure 2. The mitral valve echo is abnormal and characteristic of severe mitral stenosis. Closure of the valve and M_1 occur 0.08 second from the peak of the R wave or 0.02 second after T_1. Also shown are gallop sounds in diastole, a dilated right ventricular chamber with a poorly defined tricuspid valve and an apex cardiogram (APEX) taken at the left sternal edge consistent with right ventricular hypertrophy. IVS = interventricular septum.

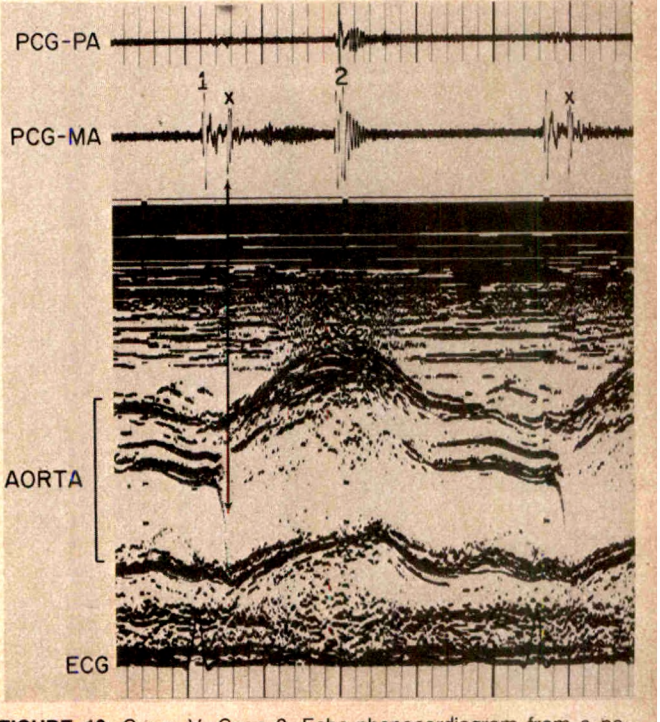


FIGURE 10. Group V, Case 2. Echo-phonocardiogram from a patient with a bicuspid aortic valve. Opening of the aortic valve is shown in the echocardiogram. The valve reaches its fully opened position at the time of the loud ejection sound (x). The presumed diagnosis of bicuspid aortic valve is based on the eccentric location of the valve cusps in diastole.[20]

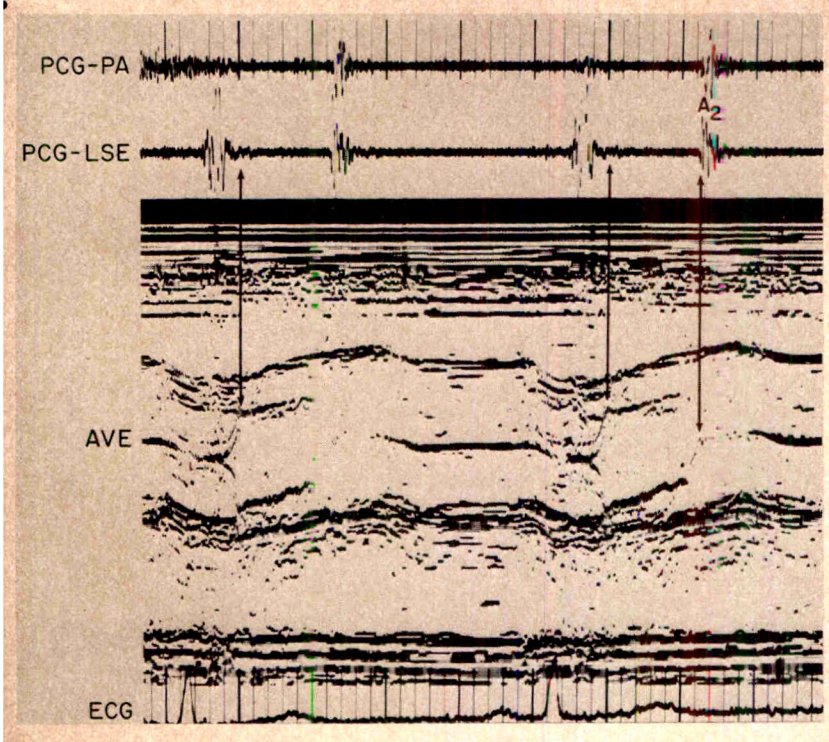


FIGURE 11. Echo-phonocardiogram from a normal subject illustrates the temporal relation between the first heart sound and full opening of the cusps of the aortic valve (AVE), indicated by the vertical line. The major components of S_1 occurred well before the full opening of the aortic valve.

tricuspid valve closure.[2] Heintzen[6] pointed out that the second major component of S_1 has its maximal intensity at the lower sternal edge, increases intensity with inspiration, and is loudest immediately after the Valsalva maneuver.[6] These findings favor the tricuspid valve or at least the right side of the heart as the main determinant of this portion of S_1. Further support for this point of view is afforded by the clinical observation of accentuation of the second major component of S_1 (T_1) in atrial septal defect,[32] and the altered relation of M_1 and T_1 in mitral stenosis.[19] A recent hemodynamic study by Lakier et al.[33] demonstrated a precise temporal relation between the second (T_1) major component of the S_1 and the peak of the right atrial C wave. They concluded that these observations provided further evidence that T_1 arises at the tricuspid valve. However, Luisada et al.[10,11] demonstrated in animal experiments that right ventricular events, including tricuspid valve closure, could not contribute to S_1 and suggested as an alternative explanation an aortic component due to aortic valve opening and sudden acceleration of blood in the root of the aorta. A similar view has been voiced by Piemme et al.[34]

Recent advances in echocardiography furnish the possibility of linking the movements of the tricuspid, pulmonary and aortic valves to various components of the S_1 complex at least temporally, if not causally. The patients we studied were selected because of audible splitting of S_1. Many of them had dilatation of the right ventricle, thus facilitating an echocardiographic study of the tricuspid valve. Although the series is not a characteristic cross section of the population, the nearly precise coincidence of the second set of high-frequency vibrations with completion of tricuspid closure was striking in both the normal subjects and the patients.

Aortic valve contribution to S_1: One of the major problems in the analysis of S_1 is the importance of events in the aortic root. The close interval between the expected time of tricuspid closure and aortic valve opening has previously made it difficult to relate the second group of high-frequency vibrations in S_1 to one or the other of these events with certainty.[35] But in certain conditions, such as ventricular pacing, bundle branch block, premature beats and other arrhythmias, asynchrony of tricuspid valve closure and left ventricular ejection might be expected to provide opportunities for separating the possible contribution of left- and right-sided events. That aortic opening may frequently contribute importantly to the production of heart sounds is well recognized.[36] Figure 10 demonstrates a loud aortic ejection sound from a patient with a bicuspid valve. An echo-phonocardiogram demonstrated the precise coincidence of this sound with the achievement of full "opening" of the abnormal valve. By contrast, in Figure 11, an echo of the aortic valve from the same patient as in Figure 1 shows that the leaflets reached a fully open position appreciably *after* the principal vibrations of S_1 had subsided, indicating in this subject an absence of aortic participation in the genesis of S_1.

Genesis of Pulmonary Ejection Sounds

Since this study is concerned with the genesis of heart sounds of possible right-sided origin, attention was given to ejection sounds in pulmonary valve stenosis and pulmonary hypertension. It is generally believed that the ejection sound in the former is "valvular" and in the latter "vascular."[12,13] These terms

suggest that vibrations resulting from the movement of the stenotic diaphragm-like valve with right ventricular systole and its halting in the root of the pulmonary artery are responsible for the ejection sound or click.[13] Findings in our three cases of pulmonary valve stenosis were consistent with this explanation. The genesis of the ejection sound in pulmonary hypertension is less clear. The "vascular" theory suggests that sudden distension of the tensely dilated root of the pulmonary artery and its branches sets this part of the cardiovascular system into vibration leading to an audible sound. If such were the case one would expect the sound to occur some time *after* pulmonary valve opening and during the period of rapid expansion of the main pulmonary artery. In 10 of 15 patients with conspicuous pulmonary sounds, Sakamoto et al.[37] found that the sound was coincident with the onset of swelling of the main pulmonary artery as registered with a transducer in the second left intercostal space; in the other 5 patients, the interval from onset of pulsation to sound was 20 msec or less.

In our patients with pulmonary hypertension no systematic effort was made to trace the distension of the pulmonary artery. However, the echo-phonocardiogram in Figure 8 demonstrates the precise coincidence of (1) the pulmonary ejection sound, (2) the achievement of a fully open position of the pulmonary valve, and (3) the *onset* of distension of the pulmonary artery as registered from the bulging movement in the second left interspace parasternally. In six of seven cases the sound itself was exactly coincident with the achievement of a fully open position of the valve. In Patient 12 of Group II, a young man with deep cyanosis and a hematocrit value of 75 percent due to a ventricular septal defect of the Eisenmenger type, the pulmonary valve reached a fully open position 0.14 second after the Q wave, whereas the ejection sound occurred 0.02 second later. It seems unlikely that the opening of an anatomically normal semilunar valve would lead to audible sound. The sudden acceleration of a mass of blood into the root of the dilated pulmonary artery immediately after opening of the valve might be the source of audible vibrations. Further observations will be needed to determine the factors that influence the temporal relations among pulmonary valve opening, acceleration of blood flow and ejection sound in various types and degrees of pulmonary hypertension.

Conclusions

We recognize the pitfalls of ascribing a causative relation to two events that happen to be simultaneous. Years ago Orias,[38] a respected expert on heart sounds, cautioned, "Each investigator using some special technic has taken account only of the factors that his particular method revealed and has ignored the existence of all that it was unable to detect." However, the experience of studying valvular and echocardiographic events in a wide variety of conditions (over 1,000 echo-phonocardiograms in the past year) indicates to us an unvarying relation between M_1 and mitral valve closure. The experience with the other three valves has been less extensive. Further study is required, taking advantage of conditions in which the several possible contributing factors in sound production can be separated. Meanwhile, our findings support the postulate that valvular events have an important place in the production of heart sounds through the mechanism of sudden acceleration or deceleration of a mass of blood when valves open or close with resulting vibrations of the cardiohemic system and audible sound.[31] This observation applies to the major events of S_1 and S_2, opening snaps of stenotic and nonstenotic A-V valves[39] and ejection sounds from stenotic and nonstenotic semilunar valves. A common mechanism may then be found for a number of apparently unrelated sounds—each of which occurs when the valve associated with its genesis has moved through its full excursion and a column of blood has been suddenly accelerated or decelerated, thus setting the cardiohemic system into vibration.

Acknowledgment

We thank Mrs. Sally Moos and Dr. Gary Burggraf for their help in the performance of the graphic studies.

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Pericardial Rub

Prospective, Multiple Observer Investigation of Pericardial Friction in 100 Patients

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A prospective, multiple observer auscultatory and phonocardiographic study of 100 patients with pericardial friction confirmed the dominant prevalence of triphasic pericardial rubs (56 percent of patients with sinus rhythm). In 9 of 33 patients with various biphasic rub patterns there was summation of the ventricular diastolic rub with the atrial systolic rub, concealing an additional 10 percent of potential triphasic friction. Fourteen of 15 monophasic rubs were audible or recordable only during ventricular systole. Rubs were best heard along the left sternal border in 84 percent of cases and tended to be louder during inspiration than during expiration; in 35 cases there was no respiratory predilection. Twenty-three rubs were palpable. Ten rubs occurred in patients with pericardial effusion, five of whom had tamponade. Extension of the neck did not have a dependable effect on rub intensity.

Detection of pericardial friction is diagnostic of acute or antecedent pericarditis in the absence of other evidence of the process.[1,2] Recognition of particular precordial bruits as friction sounds tends to be facilitated by certain distinctive auscultatory qualities and their superficiality. Precise identification of friction rubs is based on their usual tri- or biphasic distribution in the cardiac cycle and nonconformity with the characteristic locations, radiations and respiratory responses of most murmurs and thrills.[2,3] Thus, a quantitative basis is required for anticipating the behavior of pericardial rubs with respect to each of these factors.

To characterize pericardial rubs quantitatively, a prospective multiple observer study was designed to investigate their characteristics in 100 patients with pericardial friction. Because some rubs and individual rub components fluctuate within quite brief intervals[3] the investigation was limited to the time of earliest detection of the adventitious sounds. This procedure ensured uniformity of protocol and permitted study at a time in the patient's course when diagnostic precision was most important. Patients were included only if three auscultators from the Cardiology Division could be assembled simultaneously in this early period. Although other patients with pericardial rubs were examined, auscultatory and phonocardiographic data were recorded only in the consecutive 100 cases satisfying the conditions of the protocol.

Material and Methods

The senior staff and the house staff of the Lemuel Shattuck Hospital were asked to report immediately to the Cardiology Division all patients with definite or suspected pericardial disease. Pericardial friction was initially identified by auscultatory characteristics—frequent superficiality and occasional monotony of sound, with a shuffling, grating, scratching or creaking quality—and its usual occurrence, including appearance de novo, in a clinical setting in which pericarditis is known to occur. Cases were included in the study only if there was unanimous agreement that the sounds investigated were pericar-

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dial rub components. Auscultatory, palpatory and respiratory observations were made independently within a few minutes of each other by three observers, the author and two Fellows of the Cardiology Division. Unanimity was required to characterize definitively the phasic distribution of rub components—that is, which of the three major components were present: atrial systolic, ventricular systolic or ventricular diastolic. When the observers did not agree, phonocardiograms were recorded. Additional phonocardiograms were obtained in some cases for general teaching interest.

Phonocardiograms in uncomfortable or very sick patients were recorded at the bedside on portable instruments. These included: (1) three-channel Schwarzer Physioscript no. 312 with phonocardiograms at nominal filter peaks of 70, 140, 250 and/or 400 hertz at 50 or 100 mm/sec paper speed; (2) six-channel Siemens (Elema-Schönander) Cardirex with the same filters and speeds; and (3) Sanborn

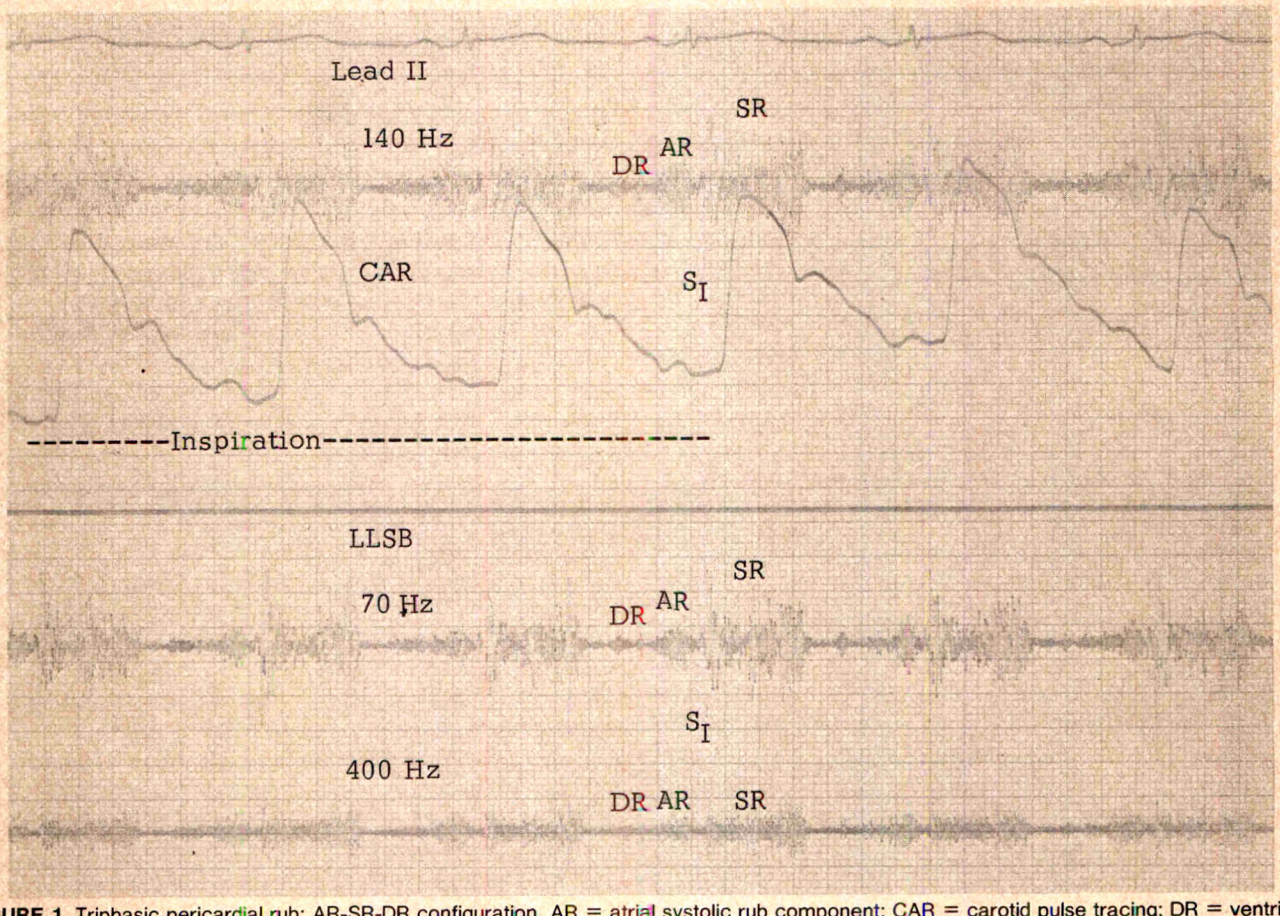

FIGURE 1. Triphasic pericardial rub: AR-SR-DR configuration. AR = atrial systolic rub component; CAR = carotid pulse tracing; DR = ventricular diastolic rub component; LLSB = left lower sternal border; S_I = first heart sound; SR = ventricular systolic rub component. There is no change in rub amplitudes during the respiratory cycle (inspiration indicated).

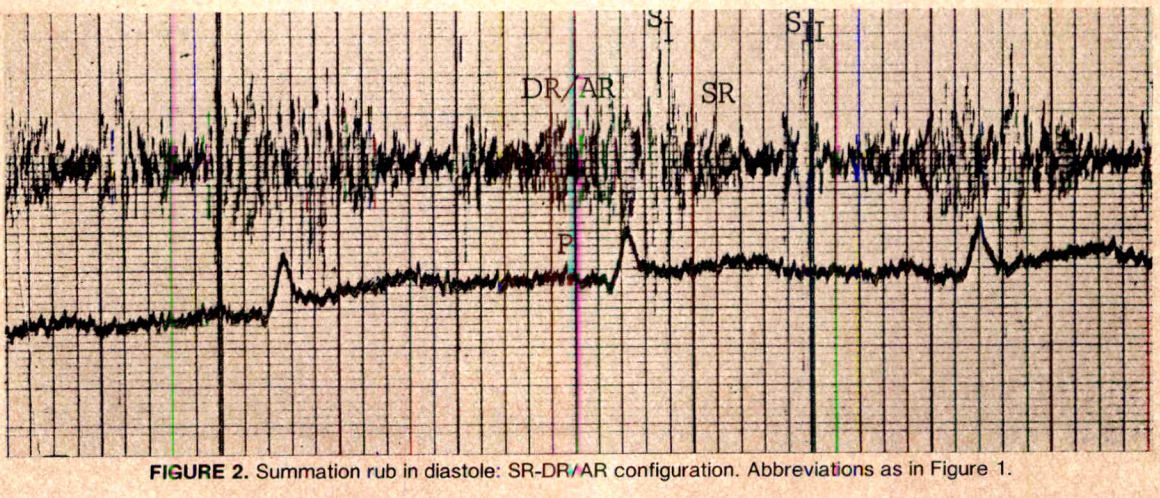

FIGURE 2. Summation rub in diastole: SR-DR/AR configuration. Abbreviations as in Figure 1.

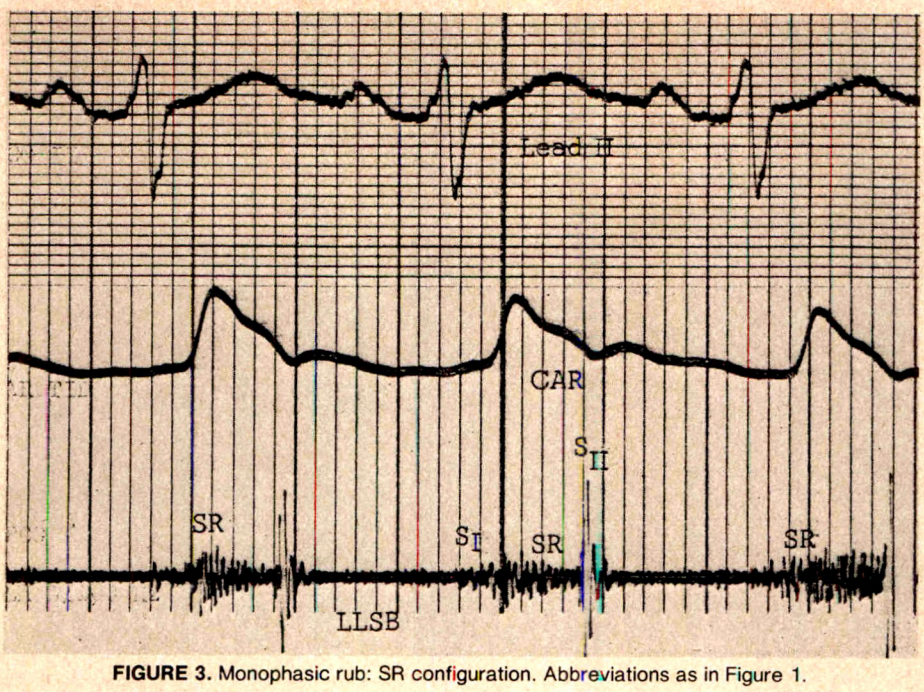

FIGURE 3. Monophasic rub: SR configuration. Abbreviations as in Figure 1.

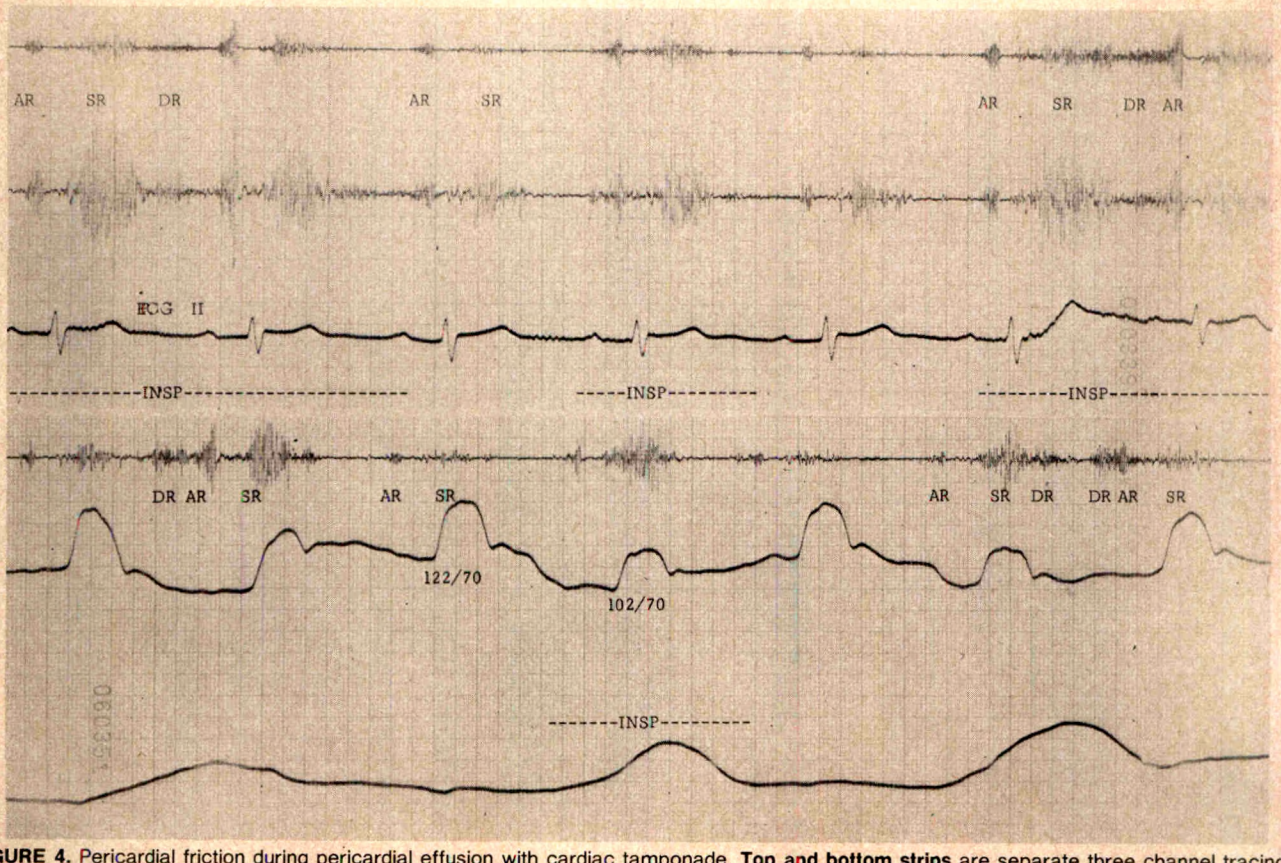

FIGURE 4. Pericardial friction during pericardial effusion with cardiac tamponade. **Top and bottom strips** are separate three channel tracings. Abbreviations as in Figure 1. Inspiration (INSP) marked (lowest recording on bottom strip is pneumogram). Middle tracing of bottom strip is carotid pulse showing pulsus paradoxus (brachial arterial pressures indicated). Pericardial rub components show great increases in amplitude during inspiration and are quite small during expiration.

TABLE I

Origin of Pericarditis in 100 Cases

Renal failure	34	
Neoplasia	20	
Radiotherapy		7
Idiopathic/uncertain origin	12	
Viral/probable viral	11	
Bacterial/probable bacterial	9	
Vasculitis/connective tissue disease	7	
Acute myocardial infarction	5	
Chest trauma	1	
Penicillin reaction	1	
Total	100	

Twin-Beam photographic phonocardiograph utilizing the logarithmic filter and 75 mm/sec paper speed. Other patients were taken to the clinical cardiac physiology laboratory for recordings on an eight channel Hewlett-Packard oscillographic recorder, series 4560, at 75 mm/sec paper speed with phonocardiograms at 200 or 400 hertz. Rubs were identified as having the components mentioned in all but a few patients. In the latter, atrial systole occurred early in diastole owing to prolonged atrioventricular (A-V) conduction and tachycardia, causing the ventricular diastolic and atrial systolic rub components to run together to produce a summation rub. Notations used to abbreviate rub components in the records and subsequently in this report are: AR (atrial systolic rub), SR (ventricular systolic rub), DR (ventricular diastolic rub) and DR/AR (summation rub). In addition to precordial auscultation and palpation, observers noted the intensity of rubs with regard to respiratory phases and areas where best heard. In 30 patients, the influence of extension of the neck was investigated by asking the patient to elevate his chin as far from his chest as he could.

Results

Table I lists the causes of pericarditis in these patients. Figures 1 to 4 illustrate most features of rubs, and Table II summarizes the phasic distributions of rub components, the range of heart rates and data in the 10 cases with rhythm and atrioventricular conduction abnormalities. Table III summarizes additional characteristics of these rubs.

Components of rubs: Table II combines the results of auscultatory interpretation by the three independent auscultators when the findings were unanimous (86 patients) with analysis of the 14 phonocardiograms recorded because of lack of unanimity. An additional 29 phonocardiograms, taken for general teaching interest, produced no contributory information. These were often obtained well after initial discovery of the rub, that is, well after the protocol time for the strictly investigational phonocardiograms. The various rub patterns occurred over a wide range of heart rates (Table II). Except in one patient with junctional tachycardia and one with atrial flutter, the heart rate did not exceed 140 beats/min. Summation rubs were produced only when the heart rate was over 100 beats/min or there was prolonged A-V conduction, or both. Seven patients had a supraventricular arrhythmia. Of the 93 patients with sinus rhythm, 52 (56 percent) had a triphasic rub (AR-SR-DR pattern, Fig. 1). Of 33 patients with biphasic rubs, 9 actually had a triphasic rub that was heard by one or more observers as biphasic because of summation of the ventricular diastolic and atrial components (SR-DR/AR pattern, Fig. 2); others heard the summation as a change in quality. All patients with prolonged A-V conduction were in this group, and in six of these phonocardiograms were required for diagnosis although at least one observer sometimes suspected summation because of the frequent increase in intensity of the rub after atrial systole. The most common biphasic rub, occurring in 16 patients, was of the atrial and ventricular systolic pattern; 8 other patients had ventricular systolic and diastolic rubs. Monophasic rubs in 15 patients included 14 during ventricular systole (SR, Fig. 3) and 1 isolated atrial rub in a patient with uremia. Thus, the ventricular systolic component occurred in 99 cases, the atrial compo-

TABLE II

Quantitative Characteristics of Pericardial Rubs (100 Cases)

Rub Phases (no.)	Cases (no.)	Rub Components	Heart Rate (beats/min) 60–79	80–99	100–119	120–140	>140
3	52	AR-SR-DR	8	25	12	7	
2	33						
	16	AR-SR	1	11	2	2	
	8	SR-DR	1*[a]	4 (1*[a])	1*[a]		2(1*[c], 1*[d])
	9	SR-DR/AR	1*[b]		4 (2*[b])	4	
1	15						
	1	AR				1	
	14	SR	1*[a]	4 (1*[a])	3	6	

* 10 patients with rhythm or A-V conduction abnormalities: a = 5 patients with atrial fibrillation; b = 3 patients with prolonged A-V conduction; c = 1 patient with junctional tachycardia; d = 1 patient with atrial flutter.

AR = atrial systolic rub; DR = ventricular diastolic rub; DR/AR = summation rub; SR = ventricular systolic rub.

nent in 78 and the ventricular diastolic component in 68 cases; both latter totals include the nine summation rubs (Table IIIA).

Other characteristics of rubs: Rubs could be louder during either respiratory phase (Table IIIB), but were more likely to be louder during inspiration (41 cases) than during expiration (24 cases) (Fig. 4). In 35 cases there was no respiratory predilection. The rubs were best heard along the left sternal border in 84 patients, and in 72 of these were best heard from the left lower to mid-sternum (Table IIIC). Table IIID records the 23 rubs that were palpable, always at the area of maximal auditory intensity and often beyond. Of these, 18 were at the left sternal border and 4 at the apex; in 1 patient the palpable rub was audible over the entire precordium, extending to the right sternal edge. Table IIIE lists 10 patients with definite or probable pericardial effusion at the time of discovery of pericardial friction; 5 of these had cardiac tamponade (Fig. 4). Table IIIF shows the effect of neck extension on rub intensity in 30 patients in whom this was investigated; there was no change in 19 instances, diminution of the rub in 7 and an increase in 4. These were always auscultatory impressions and could not be verified by phonocardiography.

TABLE III

Associated Rub Characteristics

	Cases (no.)
A. Prevalence of rub phases	
Ventricular systolic	99
Atrial systolic	69 (78*)
Ventricular diastolic	59 (68*)
B. Relation to respiratory phases	
Louder in inspiration	41
Equal in inspiration and expiration	35
Louder in expiration	24
C. Areas where best heard	
Left lower to left mid-sternal border	72
Left upper to left mid-sternal border	12
Apex	11
Right lower sternal border	4
Right mid-sternal border	1
D. Palpability	23†
E. Patients with evidence of pericardial effusion	10‡
F. Effect of extension of neck (30 patients)	
No change	19
Rub less intense	7
Rub louder	4

* Includes 9 summation rubs.
† Includes 16 of 34 patients with uremia.
‡ Includes 5 patients with cardiac tamponade.

Discussion

Auscultation and indicated phonocardiography were uniformly carried out at the apparent clinical inception of pericarditis to characterize pericardial rubs when they tended to be maximal and when their recognition *as rubs* was most necessary.

Phasic distribution of rub components: As anticipated,[1,3] triphasic (atrial, ventricular systolic and ventricular diastolic) friction was most prevalent, occurring in 52 of the 100 patients. Indeed, a triphasic rub also occurred in the nine patients with a summation rub, in whom the ventricular diastolic and atrial components were partly superimposed or run together. In six of these phonocardiograms were needed and in three the change in quality during diastole identified summation. Thus, 61 patients actually had a triphasic rub. Moreover, if one omits the 7 patients with supraventricular arrhythmias (who could not have had an atrial rub), 56 percent of the patients with sinus rhythm (52 of 93) had an obvious triphasic rub and an additional 10 percent (9 of 93) with a summation rub had a more or less concealed triphasic rub. A classic biphasic rub occurred in only 33 patients, 9 of whom had a summation rub (that is, only apparently biphasic). Thus, a truly biphasic, "to-and-fro" rub occurred in only 24 of the 100 patients. Sixteen of these patients had a clear-cut atrial and ventricular systolic rub configuration, that is, no diastolic rub. The eight other patients with biphasic friction lacked an atrial rub but had the diastolic component, that is, the ventricular systolic and diastolic pattern; five of them were among those with supraventricular arrhythmias and therefore could not have had an atrial rub. Fifteen patients had a monophasic rub of whom 14 had a ventricular systolic rub; two of these had atrial fibrillation and could not have had an atrial rub.

Triphasic or potentially triphasic rubs are clearly the rule in pericarditis and are usually recognizable as such. Rhythm and conduction disturbances were not common, but contributed to the elimination or concealment of the atrial component. Occurrence of the ventricular systolic component in 99 of the 100 cases was anticipated, since ventricular systole is the most powerful cardiac movement and hence could be expected to produce the strongest friction. On the same basis it is not surprising that the atrial rub was next most prevalent and that least prevalent was the diastolic ventricular rub, which occurs during more or less passive motion.

Other rub characteristics: There was a moderate tendency for rubs to be loudest during inspiration (41 cases) but in 35 patients there was no respiratory predilection and in 24 they were loudest during expiration. Accordingly, any rub initially confused with a murmur is unlikely to share any respiratory behavior characterizing a given murmur. The great majority of pericardial rubs were best heard along the left sternal border (84 of 100) with only 11 heard best at the apex and 5 along the right sternal border. Twenty-three rubs were palpable, at least over the areas where they were loudest, and sometimes more widely. Most of these were in patients with uremia, who generally had the loudest rubs and also the slowest heart rates. The overwhelming predilection for loudness and intensity along the left mid- to lower sternal border can

be attributed to the closeness of the heart to the chest wall at this point and to the frequent absence of interposed pleural and pulmonary tissues overlapping the heart in this zone—the so-called "triangle of safety."[1]

The finding of pericardial rubs in 10 patients with pericardial effusion confirms previous experience[3,4] that separation of parietal and visceral pericardium by fluid does not necessarily, or particularly frequently, eliminate rubs. If pericardial rubs truly are friction sounds, this implies either residual contact of the layers (probably true directly behind the heart[1,4]), friction of the external parietal pericardium with surrounding structures ("exopericardial rub" [3]), or both.

Extension of the neck is a maneuver said to increase the intensity of pericardial rubs.[1] The result in 30 of our patients was no change in 19, an increase in only 4 and an actual decrease in 7. This was, therefore, an unreliable and confusing diagnostic sign.

Acknowledgment

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Prolapse of the Posterior Leaflet of the Mitral Valve Associated with Secundum Atrial Septal Defect

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The association of prolapse of the posterior leaflet of the mitral valve with secundum atrial septal defect has recently been reported but the prevalence and features of this association have not been defined. Analysis of left ventricular cineangiograms in 54 patients with secundum atrial septal defect revealed evidence of prolapse of the posterior leaflet of the mitral valve in 20 (37 percent). In 11 patients (20 percent) there was clinical evidence of a mitral valve lesion (pansystolic murmur in 9 patients and mid-systolic click in 2 patients, 1 of whom also had a late systolic murmur); the remaining 9 patients had no auscultatory evidence of a mitral valve lesion. Thus, the incidence of clinically silent prolapse in association with secundum atrial septal defect was 17 percent (9 of 54 patients).

Analysis of the angiographic findings revealed that the prolapse was triscalloped in 4 patients, biscalloped in 11 and uniscalloped in 5. Mitral regurgitation was present in 12, including the 11 patients with clinical signs of a mitral lesion. Three patients with moderate or severe mitral regurgitation had triscalloped prolapse. The association of prolapse of the posterior leaflet of the mitral valve with secundum atrial septal defect is common and may be present in the absence of any clinical evidence of a mitral valve lesion.

Prolapse of the posterior leaflet of the mitral valve has been the subject of intense recent interest with regard to auscultatory, electrocardiographic and angiographic findings and is a well recognized cause of mitral regurgitation.[1–8] Its association with congenital heart disease, particularly secundum atrial septal defect, has also been pointed out,[3,8–12] but the frequency of this association is not known.

This study was undertaken primarily to ascertain the frequency of prolapse of the posterior leaflet of the mitral valve in association with secundum atrial septal defect. The clinical manifestations of this association, the angiographic features of the prolapse and left ventricular wall motion were also analyzed.

Material and Methods

Seventy-nine patients undergoing cardiac catheterization in the cardiovascular unit of the Toronto General Hospital between January 1970 and July 1973 were found to have secundum atrial septal defect. Fifty-four underwent left ventricular cineangiographic studies that demonstrated prolapse of the posterior leaflet of the mitral valve in 20. These 20 patients formed the basis of our study.

The clinical findings and routine right and left heart catheterization data were available for review in all patients. Cardiac output and index were calculated by the standard Fick technique. Arteriovenous difference in oxygen content across the pulmonary circulation was calculated by subtracting the oxygen content of the pulmonary artery from that of the left atrium. The arteriovenous difference across the systemic circulation was taken as the difference between oxygen content in the aorta and the average oxygen content in the superior and inferior venae cavae. Pulmonary and systemic blood flow

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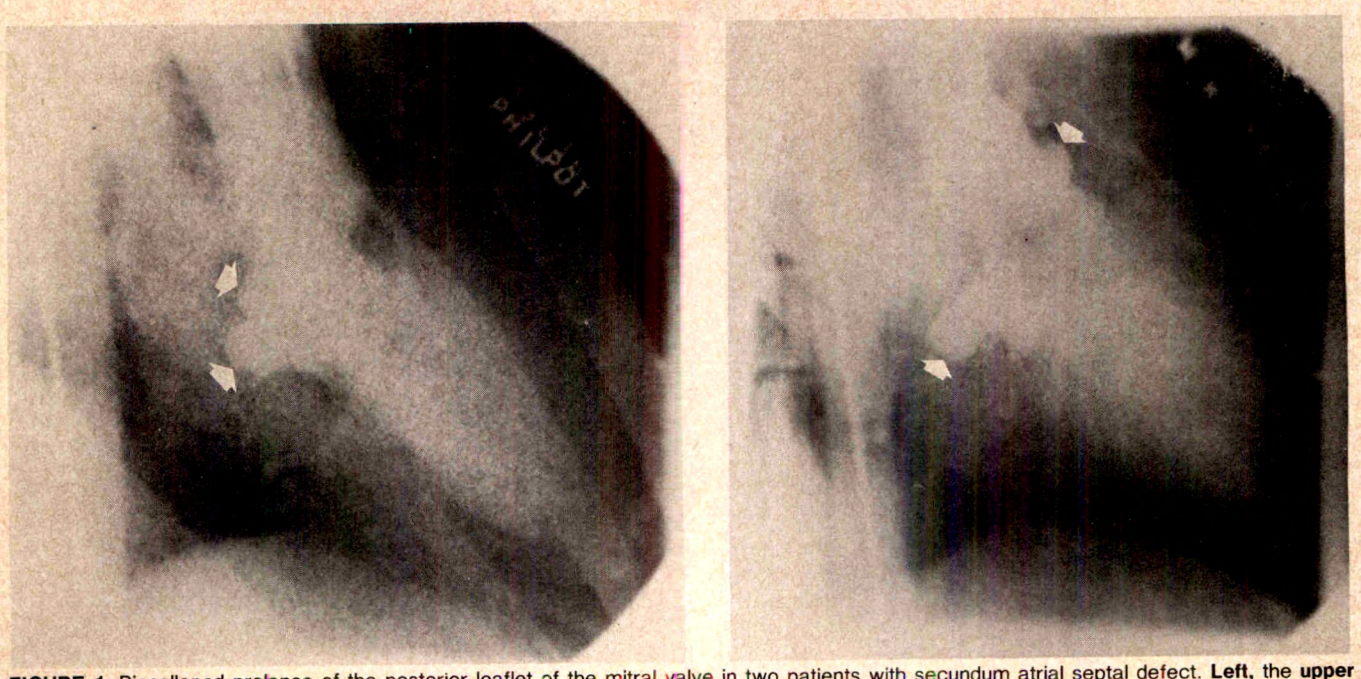

FIGURE 1. Biscalloped prolapse of the posterior leaflet of the mitral valve in two patients with secundum atrial septal defect. **Left,** the **upper arrow** points to the prolapsing anterolateral commissural scallop and the **lower arrow** to the posteromedial commissural scallop. **Right,** the **upper arrow** points to the middle scallop and the **lower arrow** to the posteromedial commissural scallop.

values and pulmonary to systemic flow ratios were calculated from these data. The left ventricular cineangiograms were obtained in the 45° right anterior oblique projection with film exposed at 30 frames/sec. Eight patients also had selective coronary cineangiograms.

Analysis of the angiographic features of the prolapse was based on a redefinition of mitral valve anatomy, carried out in this laboratory, which indicated that in 92 percent of normal hearts, the posterior mitral valve leaflet is a triscalloped structure, consisting of a large middle scallop and two smaller commissural scallops.[13] The scallop adjacent to the posteromedial commissure was called the posteromedial commissural scallop, while the scallop adjacent to the anterolateral commissure was called the anterolateral commissural scallop. As the result of angiographic-anatomic correlations in patients with prolapse of the posterior leaflet of the mitral valve,[6,7,13] it is now possible to recognize individual scallop prolapse in the right anterior oblique left ventricular cineangiogram. Prolapse of the middle scallop of the posterior leaflet produces a central bulge overlying the left atrium in the right anterior oblique left ventricular cineangiogram, whereas prolapse of the anterolateral commissural scallop causes an anterosuperior bulge and prolapse of the posteromedial commissural scallop a posteroinferior bulge[6,7,13] (Fig. 1). These criteria for recognizing individual scallop prolapse were used in analyzing the anatomic features of the prolapse of the posterior leaflet of the mitral valve in the 20 patients included in this study.

Angiographic assessment of left ventricular wall motion was carried out in 7 of the 20 patients with no mitral regurgitation and a normal cardiac index and the data were compared with those obtained from 7 normal subjects. Outlines of the left ventricular cavity were traced from the angiograms at end-diastole and end-systole. A longitudinal axis was drawn from the mid-point of the aortic valve to the apex of the left ventricle and three chords were then constructed perpendicular to and quadrisecting the long axis. These chords were designated proximal, mid-ventricular and distal segment diameters. The extent of systolic shortening was calculated for each diameter and expressed as a percent of its end-diastolic length. The ejection fraction was determined according to the ratio between stroke volume and end-diastolic volume. For these calculations, ectopic and postectopic beats were always excluded. Because all measurements taken at end-systole were referred to their end-diastolic values, correction for X-ray magnification was unnecessary.

Results

Frequency: Of 54 patients with secundum atrial septal defect undergoing left ventricular cineangiography, 20 (37 percent) demonstrated prolapse of the posterior leaflet of the mitral valve. Only 11 of these 20 patients had auscultatory evidence of a mitral valve lesion. Thus the prevalence of clinically detectable mitral valve prolapse in this series was 20 percent (11 of 54 patients) whereas that of clinically silent prolapse was 17 percent (9 of 54 patients).

Clinical findings (Table I): The mean age of the 20 patients was 43 years (range 21 to 67 years). There were 15 women and 5 men. No patient had evidence of a connective tissue disorder; four had an unconfirmed history of rheumatic fever. No patient had a history of bacterial endocarditis.

All patients had dyspnea in various degrees, but only three had heart failure at the time of hospitalization. Twelve patients gave a history of chest pain; of these, three described typical angina pectoris. In two patients the chest pain was atypical; although it was located in the anterior chest, it was not necessarily related to effort and often lasted for many hours. Seven patients described a sharp left precordial pain that was not suggestive of myocardial ischemia.

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	History: RF	Chest Pain: T	Chest Pain: AT	Chest Pain: NS	History: Pre	History: Syn	History: Palp	History: Arr	Auscultation	Electrocardiogram: ÂQRS	Electrocardiogram: RBBB	Electrocardiogram: LAE	Electrocardiogram: Inv T	Electrocardiogram: HR	Electrocardiogram: Q-T
1	48M	...	+	...	...	...	...	+	PAT	...	Ind	C	...	V_1–V_4	87	0.38^+
2	21M	...	...	...	...	...	...	...	...	...	105°	C	...	III, aVF, V_1	73	0.40^+
3	35F	...	...	...	+	...	...	...	...	Pansystolic M	120°	Inc	...	V_1	64	0.40^+
4	55M	...	...	...	+	+	...	...	...	...	105°	Inc	...	V_1	57	0.40
5	46F	...	...	...	...	...	...	+	...	Pansystolic M	−60°	C	...	V_1–V_2	80	0.40^+
6	40F	...	...	...	+	...	...	...	...	...	105°	C	+	V_1	70	0.40^+
7	47F	?	+	...	...	+	+	...	...	...	90°	...	...	III, aVF, V_1, V_2	52	0.42
8	25M	...	...	...	...	...	...	...	...	Pansystolic M	110°	C	...	V_1–V_3	93	0.32
9	36M	?	...	...	...	...	...	...	...	Pansystolic M	105°	Inc	...	V_1	70	0.38
10	45F	...	...	...	...	...	...	+	...	Pansystolic	80°	...	+	...	92	0.34
11	67F	...	...	+	...	...	...	...	...	...	100°	Inc	...	V_1–V_6	63	0.34^-
12	40F	...	...	...	...	...	...	...	...	Pansystolic	100°	Inc	+	III, aVF, V_1–V_2	70	0.38
13	26F	...	...	...	+	...	...	+	...	Midsystolic click	60°	Inc	...	V_1	67	0.38
14	24F	...	...	...	...	...	...	+	...	...	70°	...	...	V_1	86	0.34
15	58F	?	+	...	...	+	+	+	AF	Pansystolic M	140°	C	...	V_1–V_6	74	0.44^+
16	26F	...	...	...	...	...	...	...	...	...	105°	C	...	V_1–V_3	70	0.38
17	54F	?	...	...	+	...	...	+	...	Late systolic M, midsystolic click	110°	C	...	III, aVF, V_1–V_6	65	0.42^+
18	60F	...	...	...	+	...	...	+	AF	Pansystolic M	110°	C	...	V_1–V_3	81	0.40^+
19	56F	...	...	...	+	...	...	...	...	Pansystolic M	90°	C	...	V_1–V_3	77	0.40^+
20	45F	...	...	+	...	...	...	+	AF; VPB	...	80°	C	...	III, aVF, V_1–V_6	92	0.33

AF = atrial fibrillation; Arr = arrhythmia; AT = atypical chest pain; C = complete; HR = heart rate (beats/min); Inc = incomplete; Ind = indeterminate; Inv T = T wave inversion; LAE = left atrial enlargement; M = murmur; NS = nonsuggestive chest pain; Palp = palpitations; PAT = paroxysmal atrial tachycardia; Pre = presyncope; Q-T = Q-T interval (sec) (+ = prolonged Q-T, − = short Q-T); RBBB =right bundle branch block; RF = rheumatic fever; Syn = syncope; T = typical chest pain; VPB = ventricular premature beats.

TABLE II

Hemodynamic Data

Case no.	Pressures (mmHg) RA	RV	PA	LA	LV	Ao	P/S Flow Ratio	CI
1	9	31/6–9	22	11	117/2–11	111	4.3:1.0	2.28
2	6	34/1–8	20	10	107/2–10	84	2.6:1.0	2.33
3	5	28/3–7	14	6	96/1–7	82	3.0:1.0	3.73
4	5	35/5–8	20	6	126/2–12	94	1.8:1.0	4.37
5	6	46/3–8	25	10	132/2–10	111	4.4:1.0	3.51
6	7	23/0–8	15	9	110/2–11	79	3.0:1.0	4.01
7	3	27/0–6	14	5	114/2–7	90	2.2:1.0	2.77
8	9	63/3–12	40	9	104/5–11	68	3.9:1.0	2.23
9	6	35/4–9	24	8	127/0–9	101	2.6:1.0	4.44
10	2	18/1–4	14	5	105/0–5	81	2.6:1.0	2.24
11	6	70/4–12	40	8	162/2–11	110	2.9:1.0	2.43
12	3	33/2–5	18	6	118/0–5	88	2.8:1.0	1.59
13	6	27/2–6	13	9	114/1–10	85	3.2:1.0	2.80
14	4	39/0–4	28	4	106/0–9	86	2.8:1.0	2.76
15	13	70/5–13	49	14	176/0–13	127	3.0:1.0	2.47
16	11	40/5–11	25	11	122/4–12	89	5.3:1.0	2.59
17	8	76/2–8	47	8	107/3–12	90	2.2:1.0	2.97
18	10	37/2–5	22	10	124/3–9	95	5.6:1.0	1.94
19	5	42/0–6	19	7	140/2–8	90	3.9:1.0	2.50
20	3	26/0–3	13	4	114/0–4	88	3.1:1.0	2.91

Ao = mean aortic pressure; CI = cardiac index (liters/min per m^2); LA = mean left atrial pressure; LV = left ventricular pressure; PA = mean pulmonary arterial pressure; P/S = pulmonary/systemic; RA = mean right atrial pressure; RV = right ventricular pressure.

Three patients complained of presyncope on exertion and two of these had experienced syncope.

Nine patients had palpitations. Of these, one had episodes of paroxysmal atrial tachycardia and three had atrial fibrillation. One of the latter three patients also had frequent ventricular premature beats. The cause of the palpitations in the other five patients did not appear to be related to a cardiac arrhythmia.

All patients had the typical physical findings of secundum atrial septal defect, and 11 had auscultatory evidence of a mitral valve lesion. In 9 of these 11 patients, there was an apical pansystolic murmur without a click. One patient had a mid-systolic click without a murmur; the remaining patient had a mid-systolic click and a late systolic murmur.

The electrocardiogram revealed complete right bundle branch block in 11 patients and incomplete right bundle branch block in 6; there was no evidence of a ventricular conduction disturbance in 3. The frontal plane QRS loop showed clockwise rotation in all but one patient, who had abnormal left axis deviation (−60°). Right axis deviation (ÂQRS >+90°) was present in 12 patients; 5 had T wave inversion in the inferior leads (II, III, aVF); 4 had negative T waves in the left precordial leads (V_5,V_6). Repolarization changes over the right precordium were observed in all patients except those without right bundle branch block. Electrocardiographic criteria for left atrial enlargement was found in 3 patients; the Q-T interval was prolonged in 9, normal in 10 and short in 1.

Radiologic evidence of atrial septal defect (pulmonary plethora plus enlarged pulmonary arteries and right heart chambers) was found in 18 patients, but only 3 had enlargement of the left atrium suggesting a mitral valve lesion.

Hemodynamic findings (Table II): A secundum atrial septal defect with left to right shunt was demonstrated in all patients. The mean pulmonary/systemic flow ratio was 3.2:1, ranging from 1.8:1 to 5.6:1. Mean pulmonary blood flow was 14 liters/min (range 6 to 27 liters/min). Mean cardiac index was 2.8 liters/min per m^2 (range 1.6 to 4.4 liters/min per m^2). In 10 patients the mean pulmonary arterial pressure was greater than 20 mm Hg.

Both the left ventricular end-diastolic and mean left atrial pressures were normal in all but one patient. No conspicuous left atrial *V* waves were recorded.

Angiographic findings (Table III): The angiographic studies of the mitral valve revealed a triscalloped prolapse of the posterior leaflet in 4 patients, a biscalloped prolapse in 11 and a single scallop prolapse in the remaining 5. Prolapse of the posteromedial commissural scallop was seen most frequently (19 patients) followed by prolapse of the middle scallop (13 patients); prolapse of the anterolateral commissural scallop was observed in 7 patients but never occurred alone. Figure 1 demonstrates the angiographic appearance of prolapse of the individual scallops in two patients. The angiographic features of prolapse of the posterior leaflet of the mitral valve associated with secundum atrial septal defect were similar to those seen when prolapse occurred in the absence of the septal defect.[7]

Angiographic evidence of mitral regurgitation was noted in only 12 patients, including the 11 with clinical evidence of a mitral valve lesion; it was mild in 9, moderate in 2 and severe in 1. Moderate or severe mitral regurgitation was observed only in patients with triscalloped prolapse.

Selective coronary arteriograms in eight patients were normal in six and revealed minor irregularities in one; in the remaining patient with angina pectoris they demonstrated 75 percent stenosis of the left anterior descending coronary artery and 25 percent narrowing of the right coronary artery.

Left ventricular function studies (Table IV): Although shortening of the proximal diameter was reduced and shortening of the longitudinal axis was increased, the changes were not statistically significant. All individual values for ejection fraction were within normal limits, and consequently mean ejection fraction was normal and similar to the control value.

Discussion

Prevalence

The association of prolapse of the posterior leaflet of the mitral valve with secundum atrial septal defect

TABLE III

Angiographic Data

	Case no.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Prolapse																				
PMCS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	...	+	+	+
MS	...	...	+	+	+	+	...	+	+	+	+	+	...	+	+	...	+	...	+	...
ALCS	...	...	+	...	...	...	+	+	...	+	...	+	+	...	...	...	...	...	...	+
MR	1+	0	1+	0	0	0	1+	2+	1+	2+	1+	3+	0	0	1+	0	0	1+	1+	1+

ALCS = anterolateral commissural scallop; MR = mitral regurgitation (0 = nil; 1+ = mild; 2+ = moderate; 3+ = severe); MS = middle scallop; PMCS = posteromedial commissural scallop.

TABLE IV

Left Ventricular Function Studies*

	Ejection Fraction (%)	Axial Shortening (% End-Diastolic Length)			
		Longitudinal	Transverse		
			Proximal	Mid-Ventricular	Distal
Normal subjects	69.90 ± 1.17	19.90 ± 1.72	41.11 ± 2.18	40.80 ± 2.32	42.64 ± 4.04
ASD & PPLMV	67.81 ± 1.62	22.83 ± 2.19	38.31 ± 1.87	41.24 ± 2.13	42.27 ± 2.64
	NS	NS	NS	NS	NS

* Values are expressed as mean ± standard error of the mean.
ASD = atrial septal defect; NS = not significant; PPLMV = prolapse of posterior mitral valve leaflet.

has been reported by several investigators.[3,8–10,12] Hancock and Cohn[3] described this combination in 2 patients, McDonald et al.[9] in 11, Pocock and Barlow[10] in 17, Jeresaty[8] in 5 and Victorica et al.[12] in 8. However, the prevalence of this association has not previously been reported. Thus the finding that 20 of 54 patients with secundum atrial septal defect (37 percent) had angiographic evidence of prolapse of the posterior leaflet of the mitral valve is of considerable interest. It suggests that this combination of lesions is common and that evidence of mitral leaflet prolapse should be sought in all patients with secundum atrial septal defect.

Clinical Diagnosis

In 11 of the 20 patients with these lesions the mitral valve abnormality could be suspected on the basis of abnormal auscultatory findings at the cardiac apex. Nine of these 11 patients had a pansystolic murmur alone at the cardiac apex, while only 2 had a mid-systolic click, 1 of whom also had a late systolic murmur. Nine of the 20 patients (45 percent) had no auscultatory evidence of mitral valve prolapse; that is, the prolapse was silent or unsuspected. The prolapse was silent in 6 of 11 patients (54 percent) with secundum atrial septal defect and prolapse described by McDonald et al.[9] and in 4 of 8 (50 percent) described by Victorica et al.[12] Thus when both lesions are present, the associated mitral valve lesion can be suspected on auscultatory grounds in only about 50 percent of cases.

Although the frequency of auscultatory silent prolapse of the mitral valve in association with secundum atrial septal defect is high, certain features in the history and physical examination may lead one to suspect such a silent prolapse. Thus the frequency of chest pain of a typical, atypical or nonsuggestive nature was high (12 of 20 patients) in this series. Chest pain of these types has been described in patients with prolapse of the posterior leaflet of the mitral valve but is not particularly common in secundum atrial septal defect. Presyncope and syncope are also not common in secundum atrial septal defect but occur frequently in patients with mitral valve prolapse and may be related to ventricular arrhythmias.

In the electrocardiogram, the typical repolarization abnormalities found in prolapse of the posterior leaflet of the mitral valve are of limited diagnostic value in the presence of atrial septal defect. Inverted T waves in the inferior and right precordial leads coexisting with right bundle block need not represent primary changes and may be attributed to the conduction disturbance. However, negative T wave in leads V_5 and V_6 could not be interpreted on the same basis. The observation of a prolonged Q-T interval in 9 of the 20 patients may be related to delayed repolarization due to papillary muscle dysfunction.[3]

Of the nine patients with auscultatory silent prolapse in this series, eight had one or more unusual findings that might lead one to suspect the presence of the mitral valve lesion. These findings were chest pain in six, prolonged Q-T interval in three, T wave

inversion in leads V_5 and V_6 in two, syncope in one and ventricular premature beats in one.

Echocardiographic diagnosis: Definitive evidence of prolapse of the posterior leaflet of the mitral valve requires left ventricular cineangiography when the lesion is silent to auscultation. We have not made a detailed study of the echocardiographic findings but, in the future, echocardiography may be of help in recognizing auscultatory silent mitral prolapse. Minor prolapse, however, may not be detected by ultrasound (personal observations).

The combination of prolapse of the posterior leaflet of the mitral valve with secundum atrial septal defect may be diagnosed by echocardiography alone, since this technique permits ready recognition of both the prolapse and the paradoxical systolic motion of the ventricular septum and dilated right ventricle associated with the septal defect. Kamigaki and Goldschlager[14] have also described reduced velocity of opening motion of both mitral leaflets and reduced amplitude of motion of the posterior leaflet in all 11 of their patients with secundum atrial septal defect; these changes are unique to this condition.

Differentiation from ostium primum defect: Prolapse of the posterior leaflet of the mitral valve associated with secundum atrial septal defect must be distinguished from an ostium primum atrial septal defect with a cleft anterior mitral leaflet and mitral regurgitation. Although the auscultatory features in these two conditions may be similar, if not identical, the presence of left axis deviation in the electrocardiogram would strongly favor a primum defect. In addition the angiographic appearance of the left ventricle and mitral valve is quite different in the ostium primum defect[15] when compared with that described herein in prolapse of the posterior leaflet of the mitral valve associated with secundum atrial septal defect.

Surgical Treatment

Recognition of prolapse of the posterior leaflet of the mitral valve in association with secundum atrial septal defect is important because patients with prolapse are subject to life-threatening arrhythmias,[16] sudden death,[3,4,6,8] the development of severe mitral regurgitation[7,17] and bacterial endocarditis.[18,19] Antibiotic prophylaxis against subacute bacterial endocarditis is indicated in these patients both before and after surgical repair of the atrial septal defect.

Closure of a secundum atrial septal defect may increase the severity of preexisting mitral regurgitation.[20] Pocock and Barlow[10] noted the appearance of mid-systolic clicks for the first time after closure of a secundum atrial septal defect. We have observed patients who had more severe mitral regurgitation due to prolapse of the posterior leaflet of the mitral valve after closure of the atrial septal defect. It will be important to provide long-term follow-up of these patients after closure of the defect to observe what happens to the mitral valve lesion. Our study suggests that this would be particularly important in patients with triscallop prolapse of the posterior leaflet of the mitral valve, since the only patients with preoperative evidence of moderate to severe mitral regurgitation were in this group. Some of these patients may require mitral valve repair or replacement at the time of closure of the septal defect[21] depending on the severity of the mitral leak before or after correction of the septal defect. In this series of patients, the atrial septal defect tended to be large, in that the pulmonary to systemic flow ratio averaged 3.2:1 and the mean pulmonary blood flow was 14 liters/min. Closure of an atrial septal defect of this size would tend to increase the volume load on the left ventricle postoperatively, an effect that should decrease the degree of mitral regurgitation[22] but conceivably could increase it, depending on the morphologic features of the prolapse.

Etiology

The frequency of the coexistence of prolapse of the posterior leaflet of the mitral valve in secundum atrial septal defect appears to be far greater than would be expected by chance. Both conditions occur more frequently in women than in men[3,4,8] and may be of a familial nature[3,22–25] or associated with skeletal abnormalities of a Marfan-type.[3] Aside from mitral valve prolapse associated with coronary artery disease, examination of these valves at autopsy[6] or after surgical excision[7] has revealed myxomatous degeneration of the leaflets and chordae tendineae. We are of the opinion that these lesions develop independently in persons with a congenital or genetic predisposition. The secundum atrial septal defect exists from birth, but the mitral valve lesion usually manifests itself in early adult life,[8] presumably when the myxomatous degeneration in the valvular leaflet or leaflets is sufficient to cause prolapse. In our experience[6,7,26] and that of others,[23,25] myxomatous degeneration and prolapse occur far more frequently in the posterior than in the anterior mitral leaflet.

The relatively older age of the patients in this series (21 to 67 years, average 43 years) reflects the patient population of this hospital and the proximity of the Hospital for Sick Children, Toronto, which cares for children up to age 18 years. We have not personally observed prolapse of the posterior leaflet of the mitral valve in association with other congenital cardiac lesions, although others have.[10] In recent years we have been impressed that prolapse of the mitral valve as an isolated lesion is a very common cause of mitral regurgitation.

Left Ventricular Function

In this study left ventricular function was normal as judged by measurement of ejection fraction and shortening of the longitudinal and minor axes of the left ventricle. There was a slight but nonsignificant diminution in shortening of the proximal left ventric-

ular minor axis. Several investigators[27,28] have reported similar findings; others have described severe left ventricular dysfunction,[29,30] presumably at a later stage in the evolution of mitral valve prolapse.

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Effect of Digoxin on Sinus Nodal Reentry in the Dog

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The effect of digoxin on sinus nodal reentry was examined in 20 open chest mongrel dogs during infusion of digoxin at a rate of 2.5 μg/kg per min. The extrinsic cardiac nerve supply was removed acutely in 10 dogs and was left intact in the remaining 10 dogs. Sinus nodal reentry was relatively unaffected by digoxin in 18 of 20 dogs. In these 18 dogs, digitalis toxicity developed before reentry was abolished and was manifested as increased atrial and ventricular automaticity in 14 and as advanced atrioventricular (A-V) block in four. In the remaining two dogs, sinus nodal reentry was relatively sensitive to digoxin and was abolished before toxicity became manifest as advanced A-V block. The knowledge of the relative insensitivity of sinus nodal reentry to digoxin, at least in this experimental model, contrasts with the previously reported sensitivity of sinus nodal reentry to quinidine, and may be important in the management of sinus nodal reentry in man.

Atrial arrhythmias consistent with sinus nodal reentry have been observed in the dog[1,2] and man[2–4] and in isolated rabbit heart tissue.[5] The requisite conditions for reentry, slow conduction and unidirectional block, are normally present in the sinus node in early atrial diastole.[5]

Digitalis may depress conduction in the sinus node by a direct effect on sinus nodal tissue[6] and by an indirect vagotonic effect.[7–9] Thus, it was speculated that digitalis could conceivably depress sinus nodal conduction sufficiently to prevent sinus nodal reentry from occurring. It was also speculated that the vagal effect of digitalis might resemble the effect of electrical stimulation of the vagus, which has been shown to abolish sinus nodal reentry.[1,2] On the other hand, it was recognized that digitalis may actually cause reentry by its effects on conduction and refractoriness.[10]

The present study was undertaken to examine the effect of the commonly used cardiac glycoside digoxin on sinus nodal reentry in the dog.

Methods

Twenty mongrel dogs weighing 10 to 27 kg were grouped as follows:

Group 1: 10 dogs anesthetized with intravenously administered pentobarbital, 30 mg/kg body weight, and with acute extrinsic cardiac denervation. Denervation involved bilateral stellectomy and thoracic ganglionectomy from T_1 to T_4, and section of the cervical vagosympathetic trunks bilaterally. In these dogs the direct effect of digoxin on sinus nodal reentry was studied.

Group 2: five dogs anesthetized with intravenously administered alpha-chloralose, 80 to 100 mg/kg (so as to avoid the vagolytic effect of pentobarbital), in which extrinsic cardiac denervation was not performed. In these dogs we attempted to study the indirect neurally mediated effects of digoxin, especially the well known vagotonic effect of the drug.

Group 3: five dogs first premedicated with morphine sulfate, 3 mg/kg subcutaneously, and then anesthetized with intravenously administered alpha-chloralose, 80 to 100 mg/kg. Morphine was given to increase the number of dogs manifesting digoxin-induced vagotonia.[11] Extrinsic cardiac denervation was not performed in this group.

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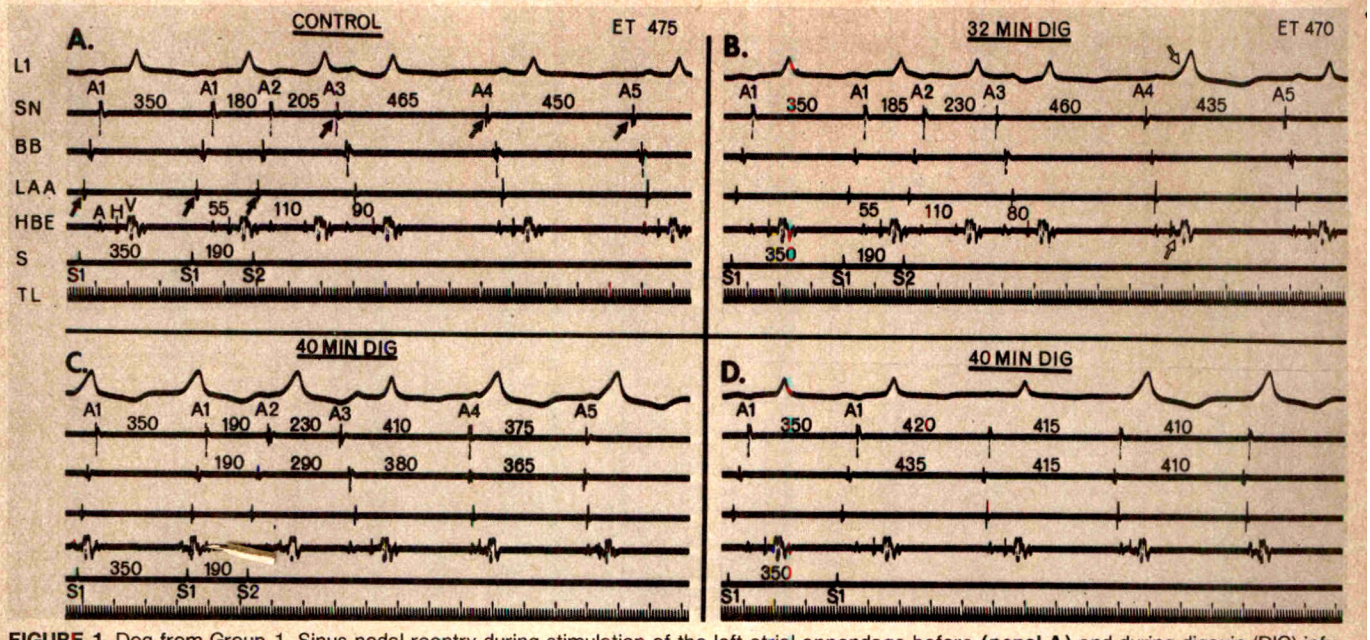

FIGURE 1. Dog from Group 1. Sinus nodal reentry during stimulation of the left atrial appendage before **(panel A)** and during digoxin (DIG) infusion **(panels B and C).** BB = Bachmann's bundle; ET = sinus nodal escape time; HBE = His bundle electrogram recorded from the low atrial septum; LAA = left atrial appendage; L1 = standard lead I; S = stimulus for the basic (S_1) and premature (S_2) beats; SN = sinus nodal region; TL = time lines recorded at 10 and 100 msec intervals. The rapid deflections are retouched in this and subsequent figures for the purpose of reproduction. Details in text.

Recording Techniques

In all animals body temperature was monitored by a rectal temperature probe and maintained at 37 ± 1° C by an electric heating pad. Teflon®-coated bipolar plunge wire electrodes[12] were inserted into the regions of the sinus node, Bachmann's bundle, coronary sinus, right atrial appendage, left atrial appendage and the low atrial septum (His bundle electrogram).

Recording and stimulating techniques have recently been described.[1] In brief, basic pacing pulses were delivered to selected atrial sites (left or right atrial appendage or coronary sinus) at a rate of 150 to 200/min. After every 10th basic beat (A_1), a premature beat (A_2) was introduced through the same stimulating electrodes and the atrial cycle scanned at decreasing coupling intervals (10 to 20 msec decrements of A_1-A_2) until the atrial effective refractory period was reached. Basic pacing pulses were omitted for approximately 1.5 to 2.0 seconds after A_2. For each basic cycle length the sinus nodal escape time was determined by omitting A_2 after the 10th basic beat.

All atrial intervals were measured from the electrogram recorded in the region of the sinus node unless otherwise stated.

After control electrophysiologic measurements were made, digoxin was infused intravenously at a rate of 2.5 μg/kg per min after administration of a priming dose of digoxin, 7.5 μg/kg.

Definition of Terms

A_1 = the atrial depolarization of a basic atrial beat.

A_2 = the atrial depolarization of an induced atrial premature beat.

A_3, A_4, A_5, etc. = subsequent atrial beats.

A_1-A_1 = the atrial interval measured during atrial pacing.

A_1-A_2 = the coupling interval measured from the last paced atrial beat (A_1) to the induced atrial premature beat (A_2).

A_2-A_3 = the interval measured from the induced atrial premature beat (A_2) to the subsequent atrial beat (A_3).

A_1-A_3 = the sum of the A_1-A_2 and A_2-A_3 intervals.

A_3-A_4, A_4-A_5, etc. = the interval between atrial depolarizations subsequent to A_3.

S_1 = the basic beat stimulus.

S_2 = the premature beat stimulus.

Results

Group 1

Characteristically, in these dogs, digoxin was ineffective in terminating sinus nodal reentry before toxicity developed (Fig. 1).

In Figure 1, a record from a typical experiment, control sinus nodal reentry is shown in *panel A.* Atrial activity was first recorded from the left atrial appendage for both the basic driving (A_1) and premature (A_2) beats, but was first recorded from the sinus nodal region for the sinus nodal reentrant beat (A_3) and for the subsequent spontaneous sinus beats (A_4 and A_5). Atrioventricular (A-V) nodal conduction time, approximated by the A-H interval, measured 55 and 110 msec for the basic and premature beats, respectively. The A_1-A_2 interval of 180 msec recorded in the sinus nodal region was 10 msec less than the S_1-S_2 interval of 190 msec. This phenomenon was due to supernormal atrial conduction for A_2 between the left atrial appendage and the sinus nodal region.[13]

In panel B, 32 minutes after onset of the digoxin infusion, early digitalis toxicity was manifested as increased ventricular automaticity (open arrows) with ventricular fusion. The small increases over control values that occurred in the A_1-A_2 (5 msec) and A_2-A_3 (25 msec) intervals were presumably due to the direct depressant effect of digoxin on conduction from the left atrial appendage to the sinus node (increase in A_1-A_2) and along the sinus nodal reentrant pathway (increase in A_2-A_3).

In panel C, after 40 minutes of digoxin infusion, in-

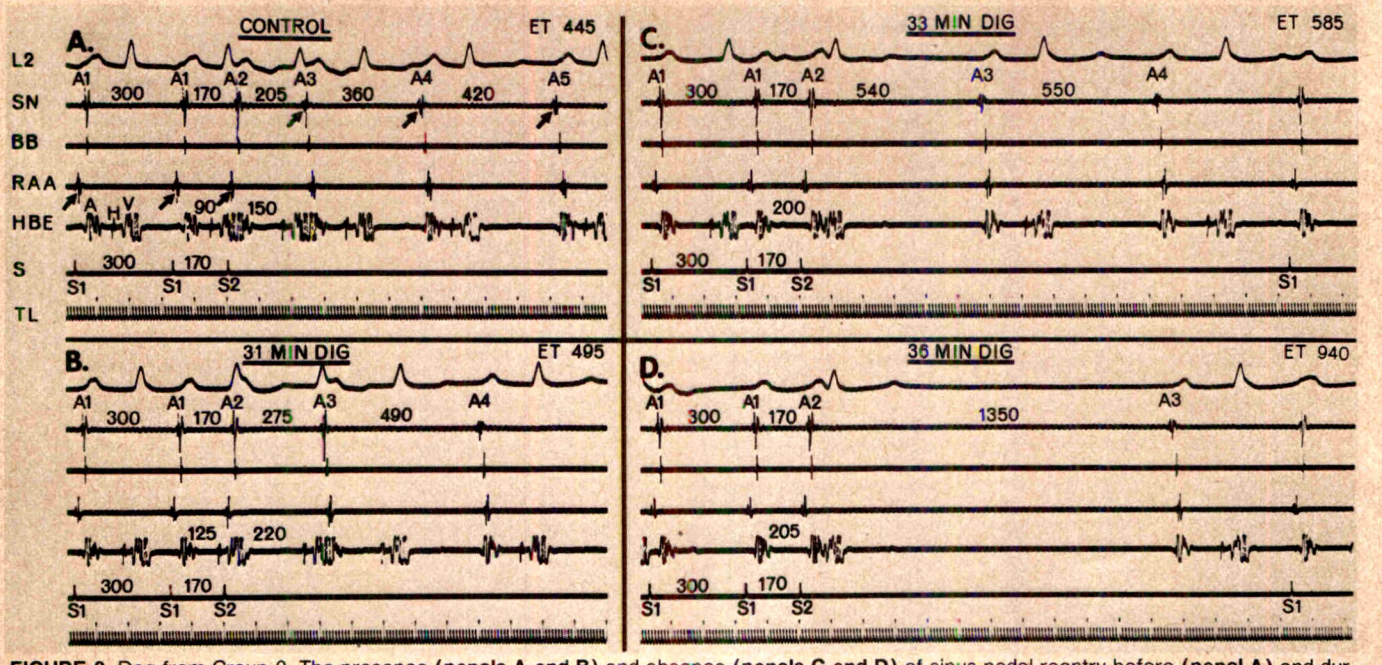

FIGURE 2. Dog from Group 2. The presence **(panels A and B)** and absence **(panels C and D)** of sinus nodal reentry before **(panel A)** and during **(panels B, C and D)** infusion of digoxin. Stimuli are applied to the right atrial appendage (RAA). Abbreviations as in Figure 1. Details in text.

creased ventricular automaticity with A-V dissociation was more evident and sinus nodal reentry was still present. Atrial automaticity, also increased at this time, was more easily appreciated when S_2 was omitted *(panel D)*.

In *panel D,* the escape time measured on the sinus nodal electrogram decreased from the control value of 475 to 420 msec. This decrease in the atrial escape time was due to the emergence of a new and more rapidly firing atrial pacemaker with an atrial activation sequence that clearly differed from the control spontaneous sinus beats. For example, in the control period before administration of digoxin (panel A), the sinus nodal electrogram preceded the Bachmann bundle electrogram for the sinus beats, whereas after 40 minutes of digoxin infusion (panel D) the Bachmann bundle electrogram preceded the sinus nodal electrogram for the ectopic atrial beats.

Thus, in these 10 dogs in Group 1 sinus nodal reentry was relatively unaffected by digoxin and could be demonstrated at the onset of toxicity in all dogs. Digitalis toxicity was manifested as increased atrial automaticity an average of 37 minutes (range 17 to 54 minutes) after the onset of infusion and as increased ventricular automaticity an average of 36 minutes (range 16 to 50 minutes) after the onset of infusion. When digitalis toxicity first appeared, the time for sinus nodal reentry measured by the A_2-A_3 interval had increased in 9 of 10 dogs an average of 31 msec (range 5 to 70 msec). Since these were denervated animals the increase was presumably due to the direct effect of digoxin in delaying conduction along the sinus nodal reentrant pathway. The atrial effective refractory period measured in eight dogs at the onset of toxicity increased in six dogs an average of 14 msec (range 10 to 30 msec) and remained unchanged in two dogs.

Group 2

In four of five dogs the response to digoxin was similar to that previously described for dogs in Group 1; that is, digoxin failed to abolish sinus nodal reentry before the development of either increased atrial or ventricular automaticity. Although in these four dogs the cardiac nerve supply was intact and chloralose anesthesia was used, vagal tone increased only minimally during the digoxin infusion. For example, when digitalis toxicity appeared the sinus nodal escape time and A-H interval had increased an average of only 5 and 9 msec, respectively. Possibly in these four dogs the stress of surgery did not allow for the indirect vagotonic effect of digoxin to become manifest.

Figure 2 illustrates the response for the single dog in Group 2 in which vagotonia did develop during digoxin infusion. *In panel A,* control sinus nodal reentry is shown after premature stimulation of the right atrial appendage. The sinus nodal escape time is 445 msec. A-V nodal conduction time for the basic and premature beats is 90 and 150 msec, respectively.

In panel B, 31 minutes after the start of the digoxin infusion, the escape time increased 50 msec, and A-V nodal conduction time increased 35 msec for the basic drive beat and 70 msec for the premature beat. Sinus nodal reentry was still present, although the time for reentry had increased 70 msec.

In panel C, 2 minutes later, the escape time increased another 90 msec, A-V nodal conduction time for the basic drive beat increased an additional 75 msec, the premature beat blocked in the A-V node, and sinus nodal reentry was abolished. The abolition of sinus nodal reentry may have been due to a vagally mediated conduction block along the sinus nodal reentrant pathway. A change in configuration of the sinus nodal electrogram for A_3 occurred when sinus

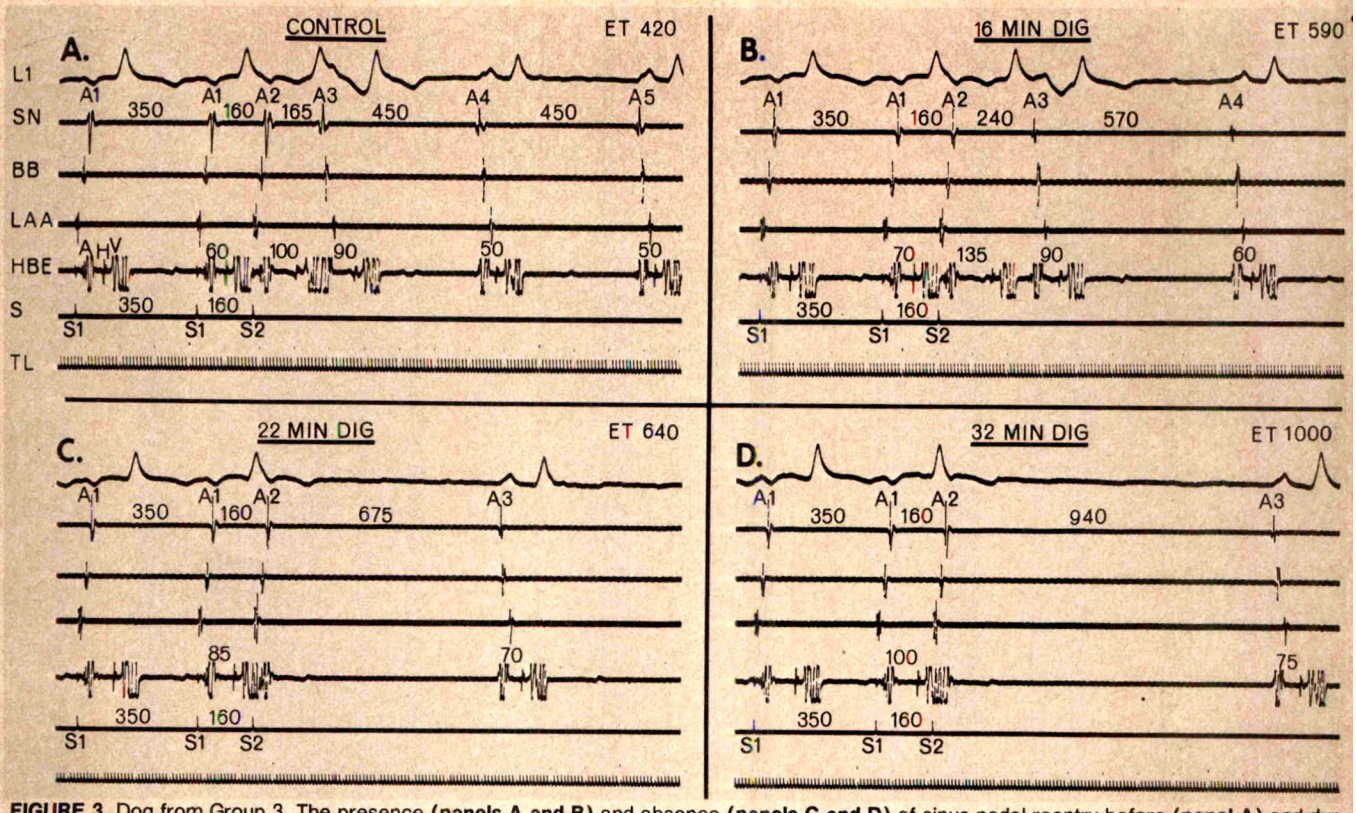

FIGURE 3. Dog from Group 3. The presence **(panels A and B)** and absence **(panels C and D)** of sinus nodal reentry before **(panel A)** and during **(panels B, C and D)** digoxin infusion. Stimuli are applied to the left atrial appendage. Abbreviations as in Figure 1. Details in text.

nodal reentry was abolished (A_3 in panel C as compared with A_3 in panel B).

In panel D, 3 minutes later, the escape time increased an additional 355 msec, second degree A-V block developed, and sinus nodal reentry remained absent. Thus, in this dog, digitalis toxicity was manifested as A-V block, and advanced first degree A-V block (panel C) was present when sinus nodal reentry was first abolished.

Group 3

All of the 5 dogs in this group had a significant increase in vagal tone during the digoxin infusion as evidenced by a progressive prolongation of the A-H interval and a significant increase in the sinus nodal escape time. The sinus nodal escape time had increased an average of 280 msec when second degree A-V nodal block developed. In three dogs, second degree A-V block developed before sinus nodal reentry was abolished. In the remaining two dogs, sinus nodal reentry was abolished during digoxin infusion before a significant degree of A-V nodal conduction delay occurred, that is before the A-H interval of the basic driving beats exceeded 100 msec (Fig. 3).

In the experiment shown in Figure 3, sinus nodal reentry was present during the control period *(panel A)* and 16 minutes after onset of the digoxin infusion *(panel B).* Six minutes later *(panel C),* and after an abrupt increase in the A_2-A_3 interval, sinus nodal reentry was abolished at this and at all other coupling intervals. When panel C is compared with the control record (panel A) it can be seen that A-V nodal conduction time increased only 25 msec for the basic driving beat when sinus nodal reentry was abolished. A-V nodal block for A_2 in panel C occurred because of a short A_1-A_2 coupling interval and not because of a significant depressant effect of digoxin on A-V nodal conduction in general. *In panel D,* further increases in A-V nodal conduction and escape times occurred and sinus nodal reentry remained absent.

Thus, in two dogs in which digoxin increased vagal tone sinus nodal reentry was abolished before a toxic degree of A-V nodal conduction delay had occurred. Presumably in these two dogs, increased vagotonia depressed conduction relatively more in the sinus node than in the A-V node and sinus nodal reentry was abolished before a significant degree of A-V block occurred.

Digitalis toxicity in the five dogs in Group 3 was manifested as A-V block. Second degree A-V block developed an average of 39 minutes (range 29 to 55 minutes) after onset of digoxin infusion and was associated in four of the five dogs with an average decrease of 16 msec (range 10 to 30 msec) in the atrial effective refractory period.

Discussion

This study indicates that sinus nodal reentry is relatively unaffected by digoxin, especially when the vagotonic effect of digoxin is minimal or absent. In two of six dogs in which the vagotonic effect of digoxin was present, sinus nodal reentry was abolished before digitalis toxicity developed.

Vagal effects of digoxin and sinus nodal reentry: Previous studies in the dog[1,2] have shown that electrical stimulation of the *right* vagus nerve consistently abolished sinus nodal reentry. It was speculated that the vagal effect of digoxin[7] might resemble the effect of electrical stimulation of the vagus nerves and thereby terminate sinus nodal reentry. However, when digitalis increases vagal tone it does so in both *right* and *left* vagi, and conduction delay can therefore be expected to occur in both the sinus and A-V nodes. If digitalis delays conduction in the sinus node to a greater extent than in the A-V node, then sinus nodal reentry might be abolished before there is a significant degree of A-V nodal conduction delay (Fig. 3). However, if digitalis delays conduction in the A-V node to a greater extent than in the sinus node, then a high degree of A-V block might occur before sinus nodal reentry is abolished (Fig. 2). Only in the first instance could digitalis be considered useful therapeutically in terminating sinus nodal reentry.

It was somewhat surprising that digoxin did not increase vagal tone in more than one of the five dogs in Group 2 with intact vagi. A possible explanation may be that the vagotonic effect of digitalis is related in part to increasing the sensitivity of the end organ, such as the sinus node, to the tonic influence of the vagus.[14] Probably because little vagal tone existed before digoxin in these open chest dogs the expected vagal effect of digoxin was not seen in four of the five dogs in Group 2. The vagotonic effect of digoxin was seen in the dogs premedicated with morphine (Group 3), which is known to act centrally to increase vagal tone.[15] Morphine may have established a resting level of vagal tone upon which digoxin could act.

Digitalis toxicity and sinus nodal reentry: In the 14 dogs (10 in Group 1 and 4 in Group 2) in which digoxin had little or no vagal effect, digitalis toxicity manifested as increased automaticity developed before sinus nodal reentry was abolished. Although in most of these dogs the time for reentry was prolonged (increase in A_2-A_3 interval) because of a conduction delay along the reentrant pathway (presumably the direct effect of digitalis), the magnitude of this delay was inadequate to terminate sinus nodal reentry before digitalis toxicity developed.

The method used to expose digitalis toxicity in this study deserves comment. Digitalis toxicity may be either manifest or concealed depending upon several factors. For example, digitalis-induced increased ventricular automaticity that becomes manifest when the atrial rate is relatively slow may become concealed when the atrial rate is relatively fast. Cessation of cardiac pacing has been shown to "unmask" digitalis toxicity.[16–18] Early stages of digitalis toxicity may be unmasked after the cessation of rapid cardiac pacing, and relatively later stages of still latent digitalis toxicity may be unmasked after the cessation of relatively slower rates of pacing. In the present study, digitalis toxicity was unmasked after the cessation of atrial pacing that ranged between 150 to 200 beats/min. Latent toxicity exposed in this manner usually preceded manifest toxicity during sinus rhythm by 5 to 15 minutes. If faster rates of atrial pacing had been used then increased atrial[19] and ventricular[20] automaticity would probably have been exposed after a smaller amount of digoxin had been given. Similarly, significant degrees of A-V block would have appeared sooner, after less digoxin, if atrial pacing had been more rapid.[17]

A corollary possibility is that digoxin might have been more effective in terminating sinus nodal reentry that was induced during sinus rhythm rather than being induced during atrial pacing as used in this study. For example, assume that digoxin increases vagal tone and decreases sinus rate. The decrease in sinus rate would tend to oppose the delay in A-V nodal conduction that might occur in response to increased vagal tone. Thus, during sinus rhythm digoxin might increase vagal tone to a point adequate to abolish sinus nodal reentry without an associated significant delay in A-V nodal conduction.

Clinical implications: Sinus nodal reentry was relatively unaffected by digoxin in 18 of 20 dogs. In these 18 dogs, 10 with extrinsic cardiac denervation, digitalis toxicity was manifested as increased atrial and ventricular automaticity in 14 and advanced A-V block in 4. In the remaining two dogs, sinus nodal reentry was relatively sensitive to digoxin and was abolished before digitalis toxicity became manifest as advanced A-V block. The knowledge of the relative insensitivity of sinus nodal reentry to digoxin, at least in this experimental model, contrasts with the previously reported sensitivity of sinus nodal reentry to quinidine,[21] and may be important in the management of sinus nodal reentry in man.

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Effects of Aminophylline on the Threshold for Initiating Ventricular Fibrillation During Respiratory Failure

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Cardiac arrhythmias have frequently been reported in association with respiratory failure. The possible additive role of pharmacologic agents in precipitating cardiac disturbances in patients with respiratory failure has only recently been emphasized. The effects of aminophylline on the ventricular fibrillation threshold during normal acid-base conditions and during respiratory failure were studied in anesthetized open chest dogs. The ventricular fibrillation threshold was measured by passing a gated train of 12 constant current pulses through the ventricular myocardium during the vulnerable period of the cardiac cycle. During the infusion of aminophylline, the ventricular fibrillation threshold was reduced by 30 to 40 percent of the control when pH and partial pressures of oxygen (PO_2) and carbon dioxide (CO_2) were kept within normal limits. When respiratory failure was produced by hypoventilation (pH 7.05 to 7.25; PCO_2 70 to 100 mm Hg; PO_2 20 to 40 mm Hg), infusion of aminophylline resulted in an even greater decrease in ventricular fibrillation threshold to 60 percent of the control level. These experiments suggest that although many factors may contribute to the increased incidence of ventricular arrhythmias in respiratory failure, pharmacologic agents, particularly aminophylline, may play a significant role.

Respiratory failure is frequently associated with cardiac arrhythmias.[1–3] Although the most common arrhythmias in this setting are supraventricular, premature ventricular depolarizations and ventricular fibrillation also occur, causing considerable morbidity and mortality. These electrophysiologic disturbances are frequently attributed to acidosis, hypoxia and electrolyte changes, but the possible role of pharmacologic agents has recently been emphasized.[4,5] One cardioactive drug frequently used in respiratory failure is aminophylline. In a series of critically ill patients sustaining cardiac arrest, Camarata et al.[5] found that aminophylline was involved in 60 percent of the cases in which a drug was a predisposing factor. This study was undertaken to investigate the effects of aminophylline on the ease of inducing ventricular fibrillation during normal acid-base conditions and during respiratory failure in dogs.

Methods

The experiments were performed in 12 adult mongrel dogs, anesthetized with sodium pentobarbital (30 mg/kg body weight) and mechanically ventilated with a Harvard pump. Catheters were placed in the femoral artery and vein for arterial and venous blood sampling and infusion of aminophylline. The heart was exposed through a right thoracotomy and suspended in a pericardial sling. A bipolar plunge electrode was secured to the right atrial wall and the sinus node crushed to allow pacing of the heart at a constant cycle length of 380 msec.

The ventricular fibrillation threshold, measured as the minimal current necessary to initiate ventricular fibrillation, was determined by a technique described previously.[4,6] Briefly, the fibrillation threshold was determined by

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passing a gated train of 12 square wave pulses, 4 msec in duration, at a frequency of 100 hertz through a right ventricular epicardial bipolar plaque electrode. This train was positioned across the vulnerable period of every 12th supraventricular beat during the same period of the electrocardiogram for each determination. The current of the train of pulses was increased by increments of 0.5 ma until ventricular fibrillation ensued. Defibrillation was accomplished within 15 seconds using a capacitor discharge direct-current defibrillator.

Respiratory acidosis and hypoxia were produced by hypoventilation employing a concentration of inspired oxygen (FIO_2) of 15 or 21 percent. Aminophylline was administered intravenously in a dose of 7 mg/kg body weight over a period of 20 to 30 minutes. Determinations of ventricular fibrillation threshold were made during and after the administration of aminophylline. The changes in threshold are shown as percent change from control values in order to normalize data from several experiments, each with a different control fibrillation threshold. Each experiment was preceded by a control period; aminophylline was not administered until the preparations were stable and three consecutive control measurements of ventricular fibrillation threshold recorded at 15 minute intervals yielded values that were within 10 percent of each other.

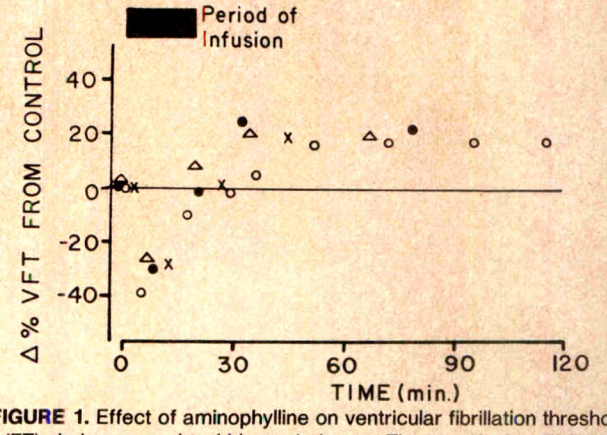

FIGURE 1. Effect of aminophylline on ventricular fibrillation threshold (VFT) during normal acid-base balance. The ventricular fibrillation threshold is plotted on the ordinate as percent change from the control value, and time is plotted on the abscissa with time zero representing the beginning of aminophylline infusion. The points plotted at time zero represent the average of the three successive control values immediately preceding the infusion. The period of infusion is indicated by the **solid bar** at top. Within 4 minutes of the initiation of infusion the threshold is decreased by 30 to 35 percent, but within 10 minutes after completion of infusion it is greater than normal. The data are compiled from four separate experiments.

Results

Normal acid-base conditions: In previous reports we have shown that the ventricular fibrillation threshold measured by the technique described is stable over the time course monitored in these studies, and that changes in threshold can be attributed to the physiologic or pharmacologic intervention.[4,6] Figure 1 shows the effect on the ventricular fibrillation threshold of intravenous administration of aminophylline (7 mg/kg) over 20 minutes. Within 5 minutes after the start of infusion, the ventricular fibrillation threshold was decreased by 30 to 35 percent, the earliest measurable decrease occurring 4 minutes after the onset of infusion. Thus, during the early phase of infusion of aminophylline, ventricular fibrillation could be induced more easily than before the infusion. However, at the end of the 20 minute infusion period, the threshold was close to control values and it eventually stabilized at a level approximately 20 percent higher than these values. This increase in ventricular fibrillation threshold persisted for 40 minutes to 6 hours.

Respiratory failure: Figure 2 shows the changes in ventricular fibrillation threshold produced by the

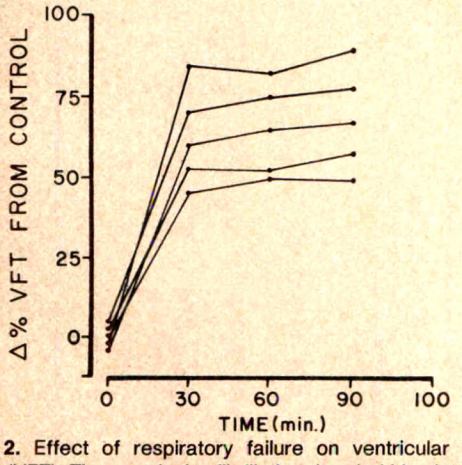

FIGURE 2. Effect of respiratory failure on ventricular fibrillation threshold (VFT). The ventricular fibrillation threshold is plotted on the ordinate as percent change from control value, and time is plotted on the abscissa as minutes from the beginning of respiratory failure. The points plotted at time zero represent the average of three successive control values during normal acid-base conditions. During the period of hypoxia and respiratory acidosis, PO_2 values were 30 to 60 mm Hg, PCO_2 values 70 to 90 mm Hg and pH values 6.8 to 7.2.

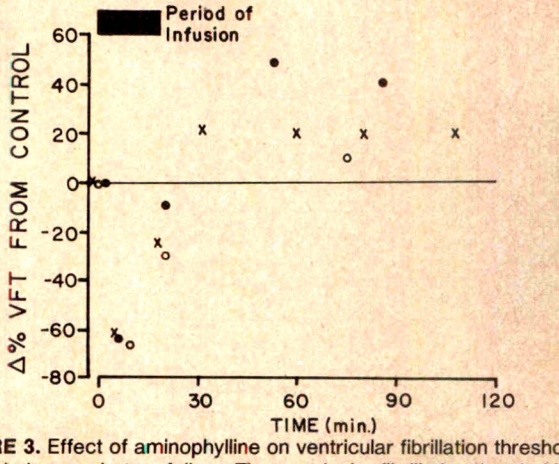

FIGURE 3. Effect of aminophylline on ventricular fibrillation threshold (VFT) during respiratory failure. The ventricular fibrillation threshold is plotted on the ordinate as percent change from control value, and time is plotted on the abscissa as minutes from the beginning of aminophylline infusion. The points plotted at time zero represent the average of three successive control values immediately preceding the infusion. The period of aminophylline infusion is indicated by the **solid bar** at top. The sequence of change in ventricular fibrillation threshold is similar to that observed during normal acid-base conditions (Fig. 1), but the decrease in threshold (during the first 5 minutes) is more marked (60 to 70 percent).

induction of respiratory failure (that is, hypoxia and respiratory acidosis) in five dogs. The control values at time 0 are the average of three successive determinations of ventricular fibrillation threshold that were within 10 percent of each other. The magnitude of the effect of respiratory failure on ventricular fibrillation threshold was variable but in all animal studies, as previously reported,[4] the threshold was increased; that is, fibrillation was more difficult to initiate.

Figure 3 demonstrates the effects of infusion of aminophylline on ventricular fibrillation threshold during respiratory acidosis and hypoxia (respiratory failure). During these experiments pH ranged from 7.05 to 7.25 and values for partial pressure of carbon dioxide (PCO_2) and oxygen (PO_2) were 70 to 100 and 20 to 40 mm Hg, respectively. As in Figure 1, a precipitous decrease in ventricular fibrillation threshold was observed within 5 minutes of the initiation of infusion but, during respiratory acidosis and hypoxia, the percent decrease in threshold was significantly greater than during periods when pH and PO_2 were normal (64 versus 32 percent). The time course of the onset and duration of the effect of aminophylline were the same as during the control conditions shown in Figure 1. The late increase in the ventricular fibrillation threshold or protective period observed after the aminophylline infusion reached approximately the same level as during the control series.

Table I summarizes data from all of the experiments described in Figures 1 through 3 involving aminophylline and respiratory failure alone and in combination. Two values for ventricular fibrillation threshold were selected for each experimental manipulation: (1) the minimal values occurring 10 minutes or less after the initiation of the experimental perturbation, and (2) the value measured after the threshold had stabilized, 30 or more minutes after the start of the experiment.

Spontaneous ventricular fibrillation during aminophylline infusion: In two animals we observed reproducible spontaneous defibrillation after infusion of aminophylline. Figure 4 illustrates one such episode that occurred while the threshold was rising above control levels. After the second supraventricular complex, ventricular fibrillation was initiated and was sustained for 2 seconds. It terminated spontaneously after three or four ventricular com-

TABLE I

Effects of Respiratory Failure and Infusion of Aminophylline on the Ventricular Fibrillation Threshold

		After Initiation of Infusion		After Initiation of Respiratory Failure		After Initiation of Respiratory Failure and Infusion	
Dog no.	Control	10 Min	30 Min	10 Min	30 Min	10 Min	30 Min
1	14.5	11.5	18.5	...	...	...	...
2	18.0	13.0	20.0	...	...	...	...
3	19.2	12.0	23.5	...	...	...	...
4	22.1	17.0	29.5	...	...	...	...
5	12.0	...	...	16.9	17.2	...	...
6	21.0	...	...	35.8	36.6	...	...
7	15.5	...	...	24.6	25.0	...	...
8	14.5	...	...	22.0	22.2	...	...
9	19.5	...	...	36.5	36.7	...	...
10	19.5	...	...	36.5	...	14.0	47.5
11	31.6	...	...	48.0	...	21.0	60.5
12	36.8	...	...	59.0	...	23.5	65.0

All values are in milliamperes of current. Control values are shown as mean values.

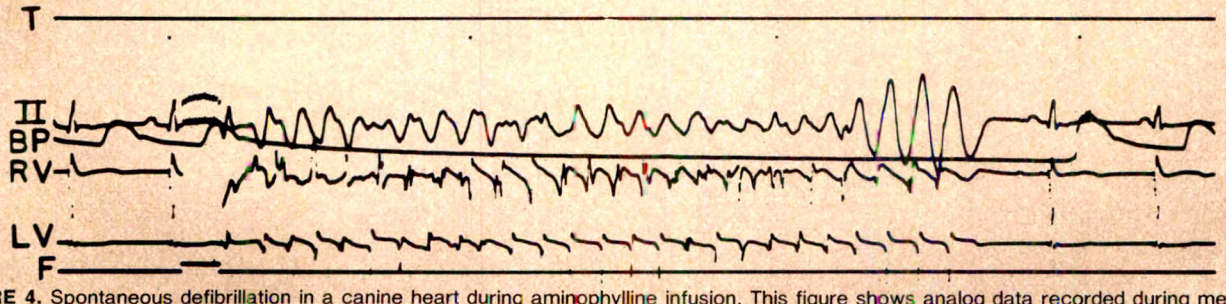

FIGURE 4. Spontaneous defibrillation in a canine heart during aminophylline infusion. This figure shows analog data recorded during measurement of ventricular fibrillation threshold and a subsequent spontaneous defibrillation, 4 minutes after initiation of the infusion. Time (T) is indicated by 1 second divisions. Lead II of the electrocardiogram (II) is recorded simultaneously with the central arterial pressure (BP), local right (RV) and left (LV) ventricular electrograms. The train of stimuli (F) does not extend beyond the absolute refractory period of the first evoked premature beat. After a 2 second period of ventricular fibrillation, organized activity resembling ventricular tachycardia precedes the return of a normal sinus mechanism.

plexes indicating apparent ventricular tachycardia. During ventricular fibrillation experiments in more than 100 dogs studies previously in our laboratory, we have observed spontaneous defibrillation of the ventricles only during the use of aminophylline.

Discussion

This study demonstrates that aminophylline exerts a biphasic effect on the ventricular myocardium with regard to vulnerability to fibrillation. During infusion it predisposes the ventricular myocardium to the initiation of fibrillation, and this effect is accentuated by the presence of respiratory failure, the clinical situation in which aminophylline is most commonly used. After completion of intravenous infusion, aminophylline exerts a protective effect on the myocardium by reducing the ease with which fibrillation can be initiated.

Mechanism of aminophylline effect on fibrillation threshold: The mechanism by which aminophylline produces the observed effects on ventricular fibrillation threshold is speculative. The effect of epinephrine on ventricular fibrillation threshold closely parallels that of aminophylline. Han et al.[7] in explaining the biphasic effects of epinephrine postulated that this agent, when administered intravenously, is initially not uniformly distributed within the myocardium. A similar nonuniform distribution of aminophylline within the myocardium would be expected to enhance disparity between the time course of recovery of neighboring ventricular fibers. This increased temporal dispersion of recovery predisposes to reentry and factionation of depolarization wave fronts, thereby facilitating the initiation of ventricular fibrillation.[8] After uniform distribution of aminophylline throughout the myocardium there would be a decrease in the temporal dispersion of recovery with the electrophysiologic parameters of ventricular fibers falling into phase. Consequently, the ventricular fibrillation threshold would be expected to increase, as observed in our experiments.

The time course of the observed effect of aminophylline upon the ventricular fibrillation threshold can be readily explained by the rate of rise of blood levels of aminophylline. Truitt et al.[9] have shown that aminophylline (7 mg/kg) administered intravenously in dogs over the time period used in our experiments results in peak blood levels in 20 to 30 minutes; blood levels then very slowly decrease to control levels over 4 to 6 hours. Therefore, the peak blood levels occur when the maximal decrease in fibrillation threshold is observed and as the threshold rises above control levels. The increased ventricular fibrillation threshold is maintained for several hours since the blood levels of aminophylline fall slowly. Presumably, when these levels are rising during the first 20 minutes of infusion, the nonuniform distribution of the drug within the myocardium increases the likelihood of fibrillation; however, when the blood level stabilizes, the distribution of aminophylline within the myocardium becomes more uniform and the initiation of ventricular fibrillation is more difficult.

Clinical implications: Although the pharmacokinetics of intravenously administered aminophylline appear similar in dog and man,[9–11] the relation between administration of aminophylline and ventricular vulnerability in man is only inferential. Determinations of ventricular fibrillation thresholds have not been made in man, and we therefore have no experience with the response of this parameter to even simple experimental maneuvers. The effect of a continuous infusion of aminophylline that eliminates the peaks encountered with an intermittent bolus regimen[12] was not investigated, but this technique holds promise as a means of avoiding the arrhythmogenic toxicity of this useful drug.

The mechanism of the potentiation of aminophylline's effects by respiratory failure observed in these experiments is not known. Cautious use of aminophylline with close observation is indicated in this condition since an increased frequency of ventricular premature beats and fibrillation may be expected. Although the effects of respiratory acidosis and hypoxia in man precipitate arrhythmias,[1–3] our observations and those of Camarata et al.[5] indicate that other factors, particularly pharmacologic agents, may facilitate the induction of ventricular fibrillation in critically ill patients.

Acknowledgment

We thank Ralph Ianuzzi for his technical assistance.

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Myocardial Imaging with Indium-113m- and Technetium-99m-Macroaggregated Albumin

New Procedure for Identification of Stress-Induced Regional Ischemia

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Regional coronary blood flow distribution was studied by myocardial imaging after intracoronary injection of technetium-99m- and indium-113m-macroaggregated albumin at rest and during coronary hyperemia induced by intracoronary injection of Hypaque-M, 75 percent. The four- to five-fold increase in coronary flow after injection of radiographic contrast material was similar in magnitude to that occurring with maximal exercise stress. Experimentally, resting coronary blood flow and regional distribution of radioactive particles remains normal in spite of coronary stenosis of up to 85 percent. Less severe stenosis causes flow and distribution abnormalities only during periods of increased flow, and the degree of maldistribution is directly related to the physiologic severity of the stenosis.

Of 49 patients with suspected coronary artery disease, 10 had no significant lesions by coronary arteriography and all had normal images at rest and during coronary hyperemia. Thirty-seven of 39 patients with significant obstructive coronary artery disease had abnormal images at rest or during contrast agent-induced hyperemia, or both. Patients with significant coronary artery disease without previous infarction usually demonstrated abnormalities in flow distribution only during coronary hyperemia. Patients with previous infarction demonstrated resting perfusion abnormalities that often became more abnormal during hyperemia. This technique provides a new method for assessing the physiologic effects of coronary stenosis in conjunction with coronary arteriography.

Myocardial imaging after intracoronary injection of radioactive particles allows the external visualization of regional blood flow distribution. Areas of diminished perfusion in myocardial images have been shown to correlate with scarring due to previous infarction[1–3] and, in some cases, with regional perfusion deficits in association with preinfarction angina.[4] Patients with normal coronary arteries or with stenosis that does not decrease resting blood flow have normal images.

Studies from this laboratory[5] and others[6–9] demonstrated that resting coronary blood flow remained normal in the presence of severe coronary stenosis. Under conditions of stress or increased flow demand, flow distal to such stenosis failed to increase. Less severe stenosis impaired the flow responses to stress (coronary reserve) to a lesser degree. Using intracoronary injections of angiographic contrast medium (Hypaque-M®, 75 percent) to increase coronary blood flow (contrast hyperemia), Gould et al.[10] demonstrated progressive maldistribution of flow as the severity of experimental coronary stenosis was increased. During periods of increased flow the degree of flow maldistribution, measured by radioactive particles, was quantitatively related to the physiologic severity of the stenosis. The presence of a regional perfusion defect during contrast medium-induced hyperemia could thus be used to detect areas of myocardium with impaired coronary flow reserve.

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We have applied this technique to patients using one isotope to study the regional distribution of coronary blood flow at rest and a second isotope to study changes in regional distribution during coronary hyperemia induced with contrast material. Reported here are the results of this study in 49 patients.

Methods

Fifty-four patients undergoing diagnostic coronary arteriography for the evaluation of ischemic heart disease were studied. All patients were fully informed of the investigative nature, potential risks and the additional time required for the imaging studies. The probability of previous myocardial infarction was clinically scaled as follows: None—no historical or electrocardiographic evidence of infarction; possible—history of severe pain, without electrocardiographic changes; probable—history typical of infarction with a normal electrocardiogram, or electrocardiographic Q wave alone; definite—typical history plus electrocardiographic Q wave and serum enzyme documentation. Coronary arteriography was performed using the Judkins technique. Contrast material (4 to 10 cc of Hypaque-M, 75 percent) was injected by hand to obtain satisfactory cineangiograms in four to six views utilizing cine and direct filming techniques. After arteriography, with the catheter in the coronary orifice, contrast material was removed and replaced with saline solution, and coronary blood flow was allowed to stabilize to a near basal level over 2 minutes.* One to 1.5 mc of either indium-113m- or technetium-99m-macroaggregated albumin (^{113m}In MAA or ^{99m}Tc MAA) was then injected into the left coronary artery over 1 to 2 seconds and flushed in with 3 to 5 cc of saline solution. Coronary hyperemia was induced with intracoronary contrast material using the same dose required for adequate angiographic visualization. Five to 8 seconds later, during the period of peak hyperemia, macroaggregated albumin tagged with the second isotope was then injected into the coronary artery over 1 to 2 seconds and flushed in with 3 to 5 cc of saline solution. After completion of coronary arteriography, biplane left ventriculography was performed with direct filming techniques.

After cardiac catheterization, the patient was taken to the nuclear medicine laboratory for imaging. Polaroid scintiphotographs were obtained in the anterior, left lateral, left anterior oblique, right anterior oblique and left posterior oblique projections with a Nuclear-Chicago HP gamma scintillation camera using a 1,000 parallel hole, medium energy collimator. In each view, 100,000 count images of each isotope (140 or 360 kiloelectron volts, 20 percent window) were recorded without any change in patient position.

Macroaggregated albumin (MAA) was prepared utilizing stannous chloride as described by Allen et al.[11]; more than 90 percent of particles were 20 to 40 μ in diameter with no particles exceeding 100 μ. A total of 30,000 to 60,000 particles for each isotope was injected. In most cases ^{113m}In MAA was given first. The MAA particle preparation and size were identical for the two isotopes, and in all patients with normal images both at rest and after hyperemia (Patients 1 to 12, Table I), images with the two agents were identical (see Fig. 2). Imaging was accomplished in 1 to 2 minutes per view for ^{99m}Tc and 2 to 10 minutes per view for ^{113m}In. Intraarterial catheter time was prolonged by 3 to 4 minutes. There were no adverse reactions to injection of MAA, and all patients are now routinely studied by this method. In two cases no MAA injections were made because of pain during each injection of intracoronary contrast medium.

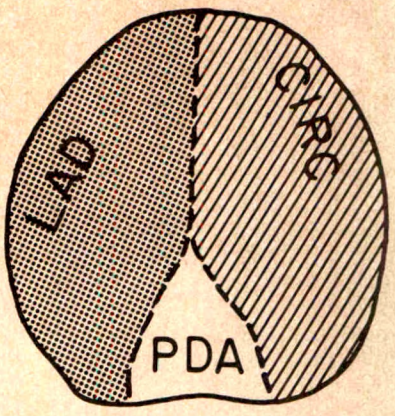


FIGURE 1. Left anterior oblique view of coronary perfusion regions. The left anterior descending artery (LAD) supplies the myocardium anteriorly, the circumflex artery (CIRC) posteriorly and the right posterior descending artery (PDA) a small inferior wedge.

Images were independently interpreted by two observers without knowledge of the clinical or arteriographic findings. Reevaluation by the same two observers demonstrated complete inter- and intraobserver agreement in all but two cases, which were excluded. Also excluded were three cases in which images were technically unsatisfactory because of nonselective injection or radiopharmaceutical breakdown.

Interpretation of the images for this study was based on the original scintiphotographs from the scintillation camera. In most cases, images were also stored on a dedicated computer system (Medical Data Systems, Ann Arbor, Mich.) for subsequent display and analysis. Examples of computer-processed data are compared with the original data in Figures 2, 3 and 6. Computer processing was used to improve image quality and provide a more quantitative approach to analysis. In each view, background subtraction, normalization of the images to the same total counts, and point by point subtraction of the image obtained during hyperemia from the image obtained at rest were performed. The resultant positive image then demarcated areas in which relative flow at rest exceeded relative flow during hyperemia, that is, showed only those areas with diminished coronary flow reserve. This type of processing facilitated image assimilation and is presented throughout.

Arteriograms were evaluated by three observers, and the percent diameter stenosis of each major coronary artery was measured. Contraction pattern abnormalities in the left ventriculogram were classified by the method of Hamilton et al.[12] as follows: normal contraction (I), borderline abnormal (II), localized hypokinesia or akinesia (III), localized dyskinesia (IV), and generalized hypokinesia or akinesia (V).

Results

Forty-nine patients had technically satisfactory myocardial images both at rest and during coronary hyperemia induced by contrast material. Table I presents data from the history, electrocardiogram, ventricular angiogram, coronary arteriogram and myocardial images for each patient. Figure 1 is a diagram

* After intracoronary contrast injection, flow increases three- to five-fold, peaking at 6 to 10 seconds and returning to the resting level over 5 to 10 minutes. Flow may be slightly increased 2 minutes after injection; but this increase is minimal compared with the 300 to 500 percent increase after injection of contrast medium.[5]

TABLE I

Data from History, Electrocardiogram, Ventriculogram, Coronary Arteriogram and Myocardial Imaging in 49 Patients

Case no.	Clinical MI Scale	Q Wave in ECG	Contraction Plot	Percent Stenosis of Coronary Arteries				Location of Image Defect	
				RCA	PDA	LAD	LCx	Resting	Stress
				1. Normal Resting and Stress Images					
1	None	None	I	0	0	0	0	None	None
2	None	None	I	0	0	0	0	None	None
3	None	None	I	0	0	0	0	None	None
4	None	None	I	0	0	0	0	None	None
5	None	None	I	0	0	0	0	None	None
6	None	None	I	0	0	0	0	None	None
7	None	None	I	0	0	0	0	None	None
8	None	None	I	0	0	0	0	None	None
9	None	None	I	30	0	0	0	None	None
10	Def	II, III, aVF	III	95	0	30	40	None	None
11	Def	II, III, aVF	II	100	0	75	0	None	None
12	Poss	None	I	100	30	80	100	None	None
				2. Resting Image Defect, No Change with Stress					
13	Def	V_1–V_3	III	0	0	100	0	Apical	No change
14	Def	V_1–V_4	IV	80	100	100	90	Anterior	No change
15	None	None	II	40	0	35	100	Infero-posterior	No change
16*	Def	V_1–V_3	III	40	70	100	80	Anterior	No change
17	Def	I, aVL	III	40	...	100	80	Antero-apical	No change
18	Def	V_1–V_4 I, aVL	V	0	0	100	45	Antero-apical	No change
19†	Poss	None	I	70	0	90	90	Posterior	No change
				3. Resting Image Defect, Additional Defect with Stress					
20	Prob	V_1–V_3	I	0	0	60 later 100	0	Infero-anterior	Defect enlarged
21	None	None	I	0	50	80	100	Infero-lateral	Infero-anterior
22	Def	I, aVL	II	100	0	70	100	Antero-inferior	Infero-posterior
23†	Poss	None	I	80	50	90	50	Infero-posterior	Defect enlarged
24*	Prob	None	II	100	0	0 (diag 80)	0	Inferior	Defect enlarged
25	Prob	None	I	100	0	100	100	Anterior	Defect enlarged
26	Def	II, III, aVF, and V_1–V_3	II	75	0	100	85	Anterior	Defect enlarged
27	Def	II, III, aVF	III	100	0	0	50	Infero-posterior	Defect enlarged
28	Def	V_1–V_5, I, aVL	IV	40	0	60	60	Infero-apical	Defect enlarged
29†	Poss	None	I	90	0	50	100	Infero-anterior	Infero-anterior and posterior
30	Def	II, III, aVF	V	100	0	80	100	Infero-posterior	Defect enlarged
31	Prob	None	II	30	0	100	0	Infero-anterior	Defect enlarged
32	Prob	None	I	100	0	100	60	Antero-posterior	Defect enlarged
33	Prob	None	III	40	0	100	100	Infero-posterior	Infero-posteroanterior
34	Def	V_1–V_3	III	50	0	100	50	Anterior	Defect enlarged
35	Prob	V_1–V_3	III	50	0	100	0	Infero-apical	Defect enlarged
				4. Normal Resting Image, Defect with Stress					
36	Prob	None	II	100	0	0	50	None	Infero-posterior
37	Poss	None	I	95	0	60	0	None	Infero-anterior
38	None	None	I	40	0	0	80	None	Infero-posterior
39	Def	II, III, aVF	II	100	0	50	50	None	Infero-anterior
40	Poss	None	I	100	...	90	100	None	Infero-posterior
41	Def	V_2–V_3	III	100	...	100	90	None	Infero-anterior
42	None	None	I	0	0	90	60	None	Anterior
43	None	None	II	100	0	60	0	None	Inferior

Continued

TABLE I (*Continued*)

Case no.	Clinical MI Scale	Q Wave in ECG	Contraction Plot	Percent Stenosis of Coronary Arteries				Location of Image Defect	
				RCA	PDA	LAD	LCx	Resting	Stress
			4. Normal Resting Image Defect with Stress (continued)						
44	None	None	I	0	0	65	35	None	Infero-apical
45	Poss	None	I	0	0	60	80	None	Anterior
46	Poss	None	I	0	0	70 (diag 90)	40	None	Antero-posterior
47	Poss	None	I	100	0	50	0	None	Antero-posterior
48	Def	II, III, aVF	II	90	0	50–60	0	None	Infero-posterior
49	Prob	None	II	100	0	75	100	None	Infero-posterior

* Right coronary image.

† Preinfarction angina.

Clinical MI (Myocardial Infarction) Scale: history of infarction as defined under Methods—Def = definite, Prob = probable, Poss = possible; diag. = diagonal branch; ECG = electrocardiogram; LAD = left anterior descending artery; LCx = left circumflex artery; PDA = posterior descending artery; RCA = right coronary artery.

of the perfusion areas in the left anterior oblique view, which provides the best delineation of abnormalities. In this view, the left anterior descending coronary arterial distribution is visualized anteriorly, the circumflex distribution posterolaterally and the posterior descending distribution inferiorly.

On the basis of resting and hyperemic images, patients were grouped into four categories as follows:

1. Normal myocardial images at rest and during coronary hyperemia: Twelve patients (Cases 1 to 12) had uniform perfusion of the left ventricular myocardium at rest and demonstrated no change in perfusion pattern during coronary hyperemia. An example of findings in a patient with no coronary disease and normal images at rest and during stress is shown in Figure 2. Computer processing and subtrac-

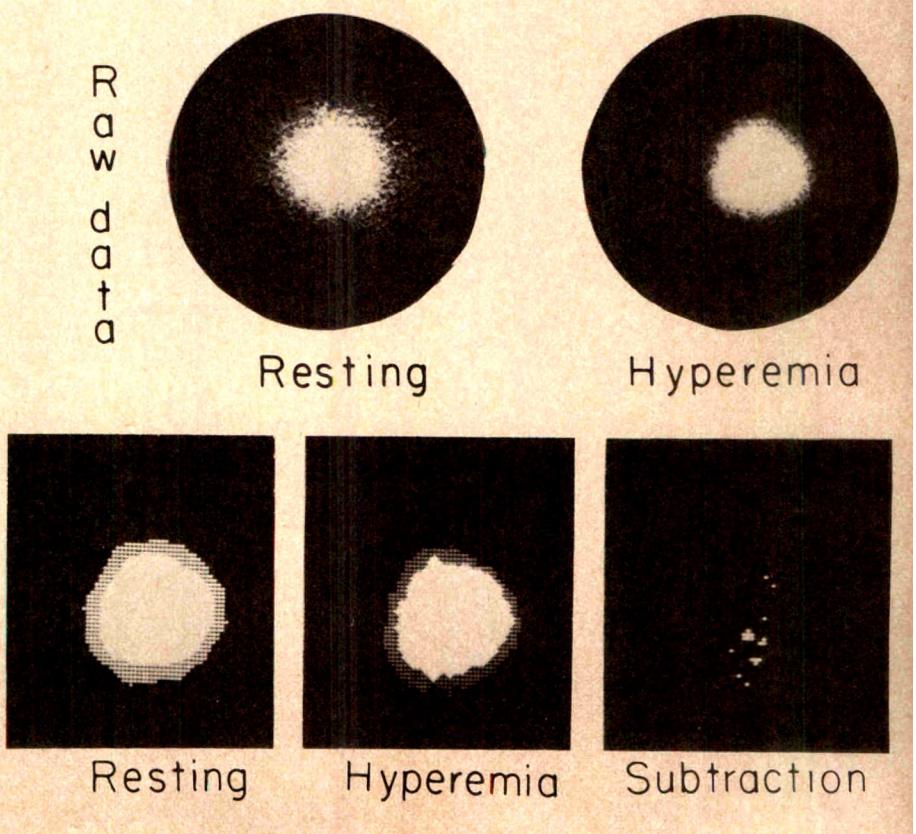


FIGURE 2. Case 6. Patient with normal coronary arteries by arteriography. The images at rest are normal and there is no change in the perfusion pattern during hyperemia. Both the original scintiphotographs **(top)** and the computer-manipulated images **(bottom)** are shown. The computer subtraction image shows insignificant amounts of activity.

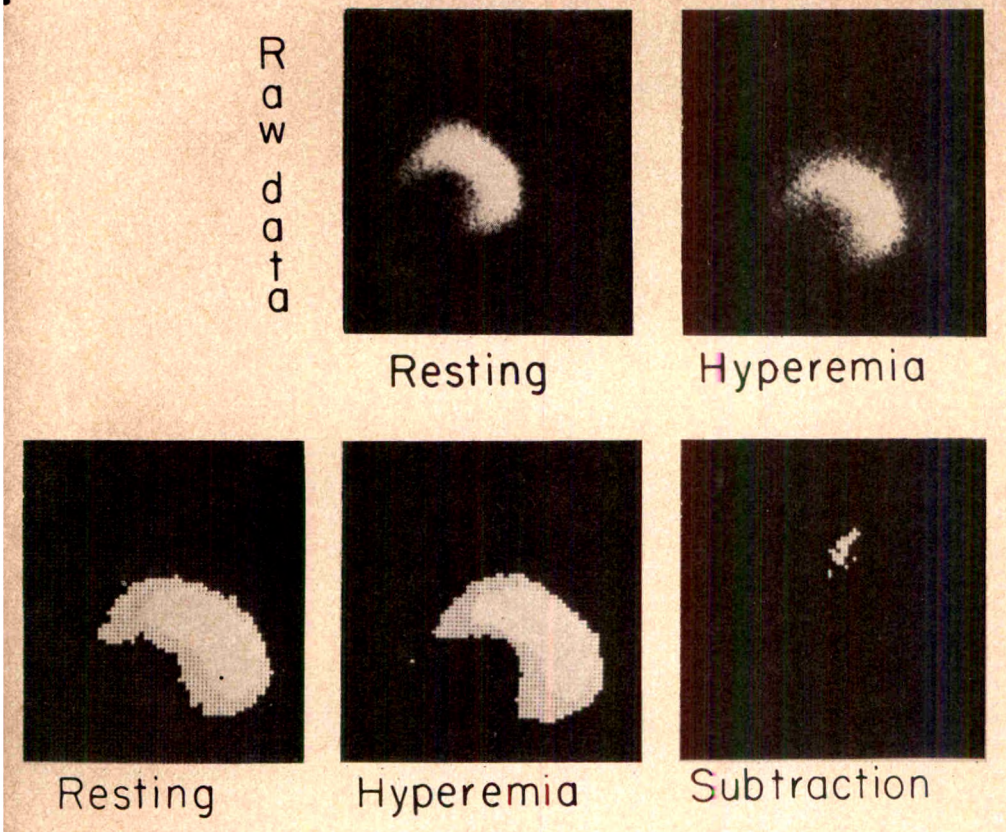


FIGURE 3. Case 18. Patient with total occlusion of the left anterior descending coronary artery accompanied by anterior infarction. Both the original scintiphotographs **(top)** and the computer-manipulated data **(bottom)** show a large anterior defect that does not change during hyperemia. Failure of the perfusion pattern to change is confirmed by the computer subtraction image.

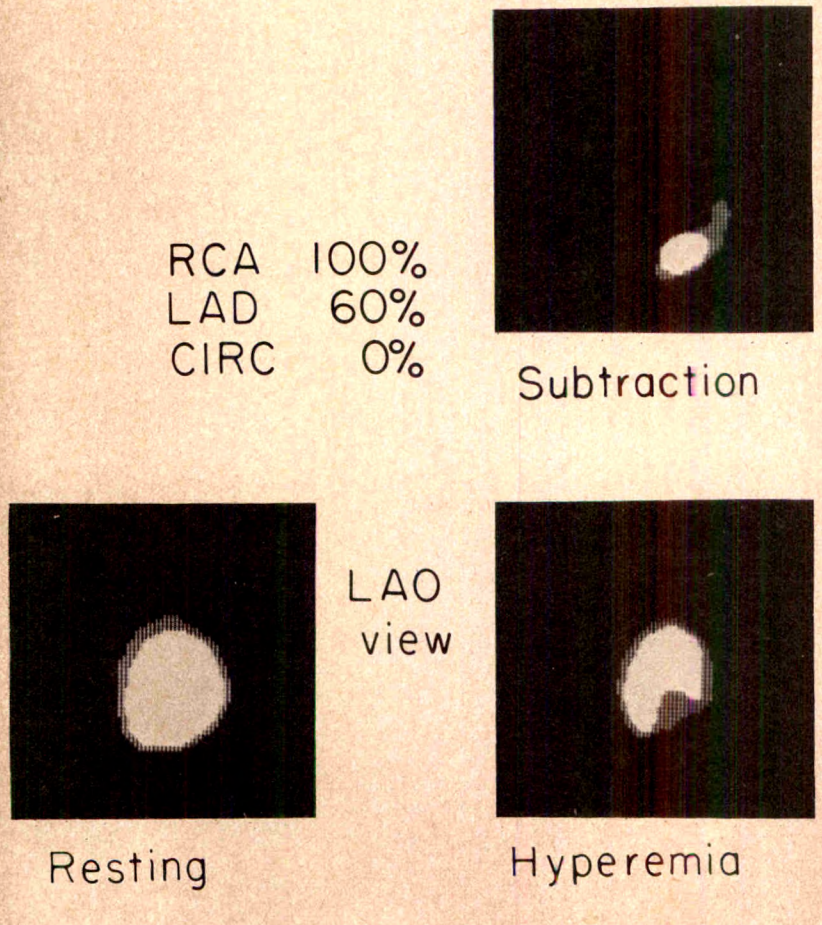


FIGURE 4. Case 22. Patient with an abnormal resting study and an additional inferior defect during hyperemia. The resting apical defect is not appreciated in the left anterior oblique (LAO) view, but this view showed the inferior defect most dramatically. CIRC = left circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

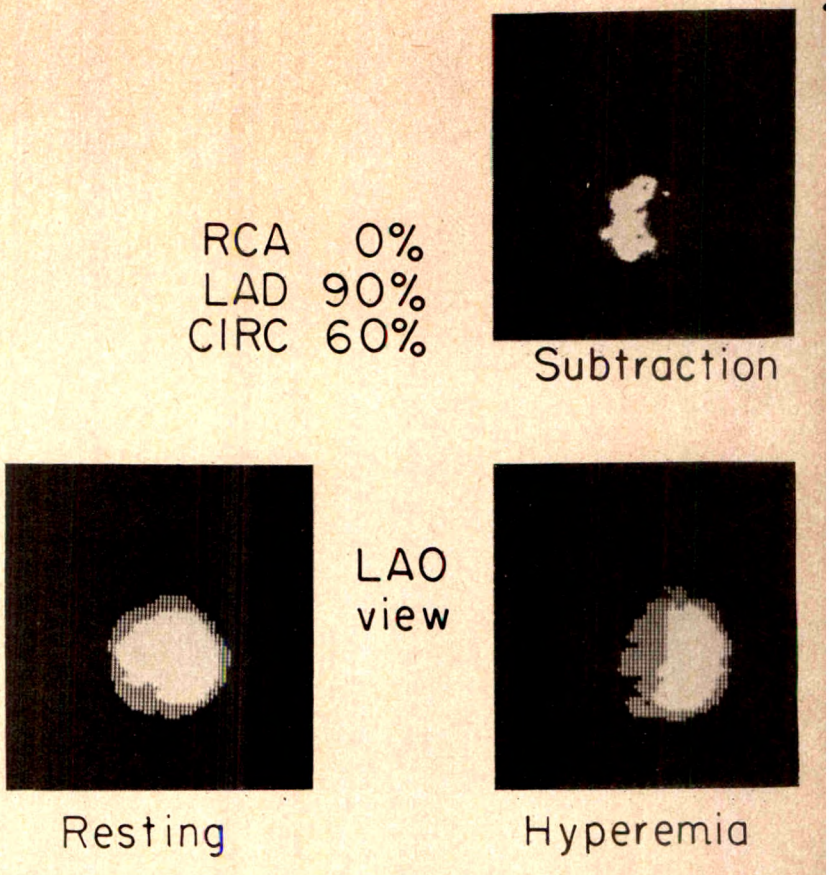


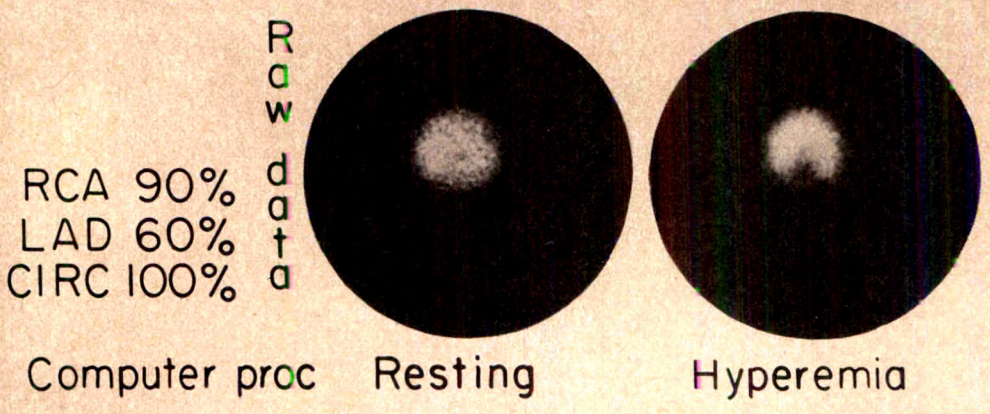
FIGURE 5. Case 42. Patient with lesions in both the left anterior descending and circumflex coronary vessels. In spite of the severe stenosis, the resting perfusion pattern is normal. During hyperemia there is pronounced malperfusion of the anterior myocardium supplied by the left anterior descending artery.

tion of the image obtained during hyperemia from the image obtained at rest revealed no significant change in regional distribution during hyperemia. None of the patients in this group had electrocardiographic or ventriculographic evidence of infarction. In 10 of the 12 patients, the left coronary system was normal or showed less than 40 percent stenosis. Two patients (Cases 11 and 12) had normal images during hyperemia in spite of apparent severe coronary stenoses by arteriography.

2. Abnormal myocardial images at rest with no change during coronary hyperemia: Seven patients (Cases 13 to 19) had image defects in the resting study and no further change during hyperemia. Results in a patient with a large anterior wall defect at rest are shown in Figure 3. No change in the perfusion pattern during hyperemia was appreciated in the raw data and this finding was confirmed by the computer-processed images. Most of this group (five of seven) had previous infarction based on history, electrocardiogram and ventriculogram. Two patients (one with preinfarction angina) demonstrated resting perfusion defects without other evidence of infarction.

3. Abnormal image at rest with further perfusion abnormality during coronary hyperemia: Sixteen patients (Cases 20 to 35) had image defects at rest and additional defects during hyperemia (Fig. 4). The majority of this group had evidence of previous infarction at the location of the perfusion defect. Two of the three patients without evidence of infarction had preinfarction angina.

4. Normal image at rest with the appearance of a perfusion defect during coronary hyperemia: Fourteen patients (Cases 36 to 49) with normal images at rest manifested defects during hyperemia. Figure 5 is from a patient with a normal resting image in spite of 90 percent stenosis of the left anterior descending coronary artery and 60 percent stenosis of the left circumflex artery. After hyperemia, there was an anterior perfusion defect demonstrating that coronary flow reserve was more severely impaired in the distribution of the left anterior descending coronary artery than in that of the circumflex artery. Figure 6 illustrates data in a patient with a normal perfusion pattern at rest who manifested a prominent inferior myocardial wall perfusion defect during hyperemia. In addition, computer processing demonstrated a posterior myocardial wall perfusion defect that was not readily apparent in the initial scintiphotographs. Figure 7 depicts findings in a patient with 80 percent stenosis of the distal circumflex coronary artery. The resting image was normal but during hyperemia a posterior wall perfusion defect was seen. In both of these cases computer processing provided more precise anatomic localization than did the initial scintiphotographs. On the basis of history, electrocardiogram and ventriculogram, 12 patients in this group had no evidence of prior myocardial infarction in the left coronary system. A single patient



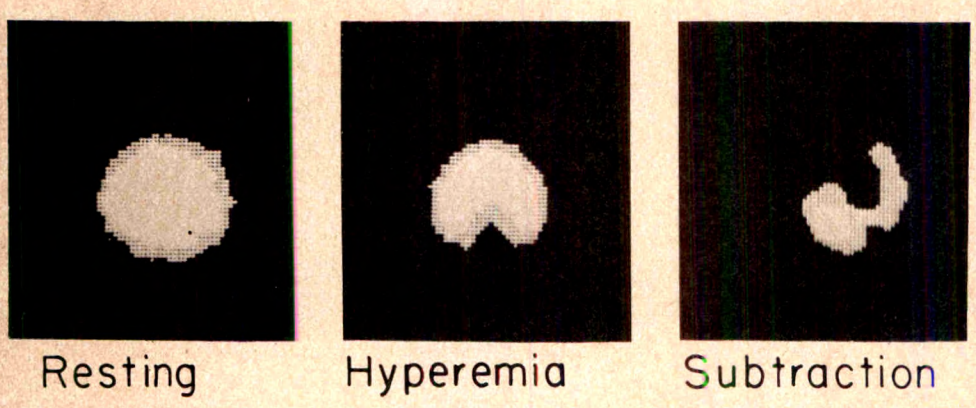
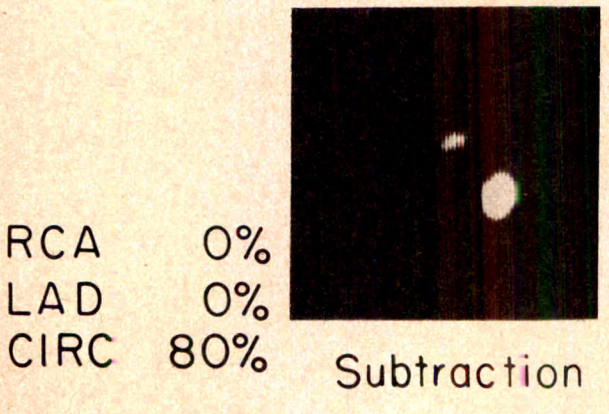


FIGURE 6. Case 48. Patient with three vessel coronary disease with a normal perfusion pattern at rest. During hyperemia an inferior wall defect develops which is easily appreciated in both the original scintiphotographs **(top)** and the computer-processed images **(bottom).** The computer subtraction image shows that there are in fact hyperemic perfusion defects inferiorly and posteriorly. The posterior defect coincides with the circumflex lesion and demonstrates the utility of computer processing in detecting lesions not readily apparent in the raw data.



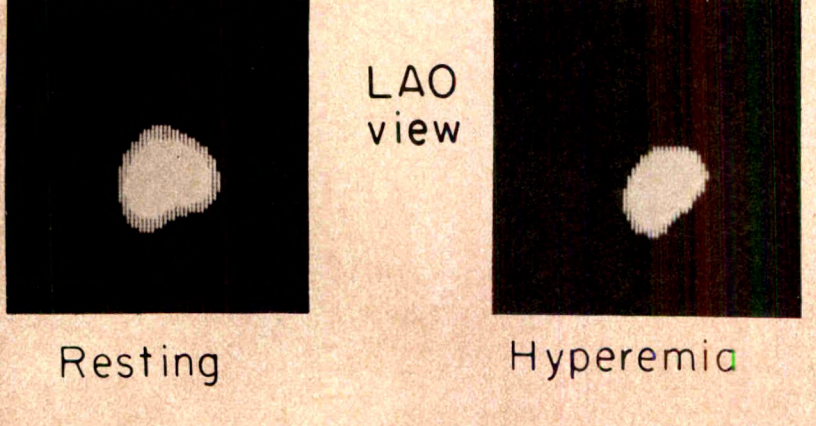


FIGURE 7. Case 38. Patient with a single stenosis of the left circumflex coronary artery. At rest perfusion is normal; during hyperemia a defect in the posterior myocardium develops.

(Case 41) with clear evidence of previous infarction had a normal resting image. In each case, the artery supplying the area of the stress-induced perfusion deficit demonstrated stenosis of 50 percent or greater.

Of the total group of 49 patients, all 10 with no or insignificant left coronary lesions (less than 50 percent stenosis) had normal images both at rest and during hyperemia. Of the 39 patients with significant disease of the left coronary system (more than 50 percent stenosis), 37 demonstrated perfusion abnormalities. Fourteen manifested abnormalities only during hyperemia and 7 only at rest; 16 with abnormalities at rest manifested further perfusion defects during hyperemia.

Discussion

Hemodynamically significant coronary arterial lesions impair regional blood flow at rest or during periods of increased oxygen demand. To assess fully the significance of a given coronary lesion or lesions, it is necessary to determine the extent and location of (1) segments of myocardium irreversibly scarred from prior myocardial infarction, (2) segments of viable myocardium with diminished resting blood flow, and (3) segments of myocardium with normal resting blood flow that became ischemic during stress.

This study documents the feasibility of using dual isotope, intracoronary macroaggregated albumin imaging to detect impaired regional blood flow distribution during periods of increased coronary flow. Experimentally, increased coronary flow can be stimulated by exercise, temporary coronary occlusion,[13] isoproterenol infusion,[14] pacing,[15] or intracoronary injection of Hypaque-M, 75 percent.[5] Hypaque was the most convenient stimulus to utilize since each patient required identical intracoronary injection of contrast medium for arteriography. Intracoronary contrast material increases coronary flow four- to five-fold; this increment in flow is similar in magnitude to that seen with physiologic stimuli and thus serves as a stress equivalent.[5,10] The coronary hyperemia induced by contrast material is related to this agent's high osmolality.[16] Contrast material is not a "stress" in the usual sense in that myocardial oxygen consumption is not increased and for this reason may be safer to use than other stimuli.[17]

Physiologic basis for technique: The physiologic basis for this technique has been reported by Gould et al.[5,10] Neither resting coronary blood flow nor coronary reserve (the hyperemic flow response to contrast material or other stimuli) was affected by stenoses less than 45 percent in diameter. Stenoses 45 to 85 percent in diameter progressively diminished the coronary reserve although resting blood flow remained normal. Higher grade stenoses decreased resting flow and abolished coronary reserve. The increment in coronary flow after injection of Hypaque was directly predictive of the magnitude of stenosis and could be quantified with dual radioisotope macroaggregated albumin injections.[10]

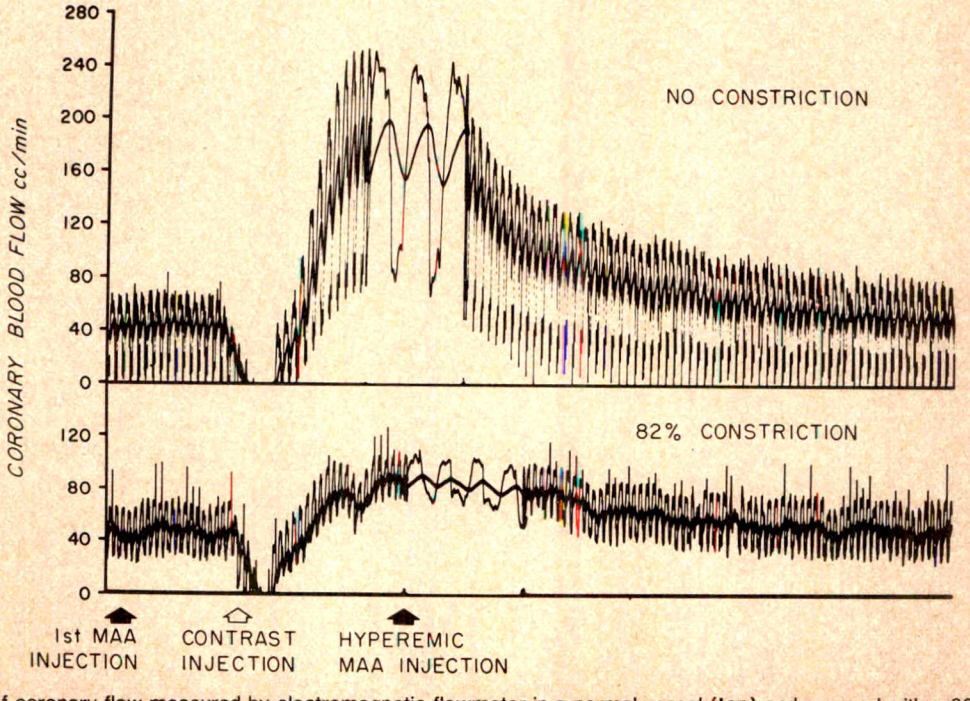


FIGURE 8. Tracing of coronary flow measured by electromagnetic flowmeter in a normal vessel **(top)** and a vessel with a 82 percent diameter constriction **(bottom).** The response of both mean and phasic flow are shown at rest and after intracoronary contrast injection. The first injection of MAA, made at rest, will be equally distributed to the normal and the constricted vessel because flow rates are similar in both vessels **(left arrow).** After injection of contrast medium **(center arrow),** the hyperemic response in the normal vessel greatly exceeds that in the constricted vessel. The relative distribution of MAA injected during hyperemia **(right arrow)** will then reflect the magnitude of hyperemic flow in the two vessels, creating an image defect in the bed of the constricted vessel. (Adapted by permission from Gould et al.[5])

Figure 8, adapted from the experimental canine study of Gould et al.,[5] illustrates the physiologic principle of the dual isotope imaging technique. Phasic and mean coronary flow in a normal vessel and a vessel with 82 percent constriction are depicted before and after intracoronary injection of contrast material. The flow in both vessels is identical and normal at rest. Since flow is normal in both vessels, macroaggregated albumin injected at rest will be equally distributed to both vascular beds. After intracoronary injection of contrast medium, there is a five-fold increase in blood flow in the normal vessel compared with a two-fold increase in the constricted vessel. Macroaggregated albumin injected at this point will be maldistributed in a ratio proportionate to the altered hyperemic response. Thus, perfusion defects detected at rest represent regions of diminished resting coronary blood flow, whereas defects present only in images injected during hyperemia demonstrate reduced coronary flow reserve.

Other techniques applicable to patients have evaluated coronary flow in the resting state and failed to distinguish consistently between patients with severe coronary stenoses and normal subjects.[18–20] Two studies utilizing pacing or isoproterenol stress demonstrated decreased coronary reserve in patients with coronary disease, but the techniques did not allow precise anatomic delineation of regional flow distribution.[15,21] Other radionuclide imaging techniques, such as those using potassium-43, may identify myocardial ischemia, although the physiologic mechanisms are incompletely understood.[22] Regional perfusion abnormalities were identified with the injection of ^{43}K during exercise only when other indications of ischemia, namely, S-T segment depression and angina pectoris, were present.[23] Poor image resolution and high costs limit use of this technique.

Clinical results: In this series 75 percent (30 of 40) of all patients with arteriographically proved coronary artery disease manifested new myocardial perfusion defects in the study performed during coronary hyperemia. In 10 of these cases, perfusion defects were associated with arteriographic stenoses 50 to 60 percent in diameter. The arteriogram cannot accurately predict which, if any, stenoses in this group of patients with milder lesions will have hemodynamic consequences during stress. Direct physiologic consequences—namely, regional malperfusion during increased flow demand—were demonstrated with the dual isotope technique. In 16 patients with resting perfusion abnormalities, contiguous perfusion abnormalities were identified during hyperemia. In these patients, other indications of muscle viability were generally lacking, most patients having complete occlusions with variable visualization of the distal bed, electrocardiographic Q waves and abnormalities of contraction pattern (Table I).

Reliability and limitations of technique: All patients with image defects during coronary hyperemia had associated arteriographic stenoses 50 to 100 percent in diameter; there were thus no identifiable false positive defects. Four patients (Cases 12, 14, 17 and 19) had high grade proximal stenoses of both the circumflex and left anterior descending coronary arteries but had no associated contrast agent-induced image defects. In cases with nearly equal stenoses or with complete occlusion in one vessel and a high grade stenosis in the second, coronary reserve may be uniformly depressed. For example, if the left anterior descending and circumflex arteries have equal stenoses, the response to hyperemia will be equally depressed in both arteries and maldistribution will not occur. The right coronary artery has no large proximal branches, and proximal stenoses may similarly depress coronary flow reserve throughout its bed. These observations reflect an important limitation of the technique, namely, that relative rather than absolute flow is assessed as previously demonstrated experimentally.[10] An additional patient (Case 11) had an isolated 75 percent stenosis of the left anterior descending coronary artery with normal resting and stress myocardial images. One would have predicted a hyperemic image defect; its absence could be related to technical factors such as improper timing of isotope injection or to erroneous interpretation of the angiograms. In all other cases, stenosis of 60 percent or greater was detectable as a hyperemic image defect; if a 60 percent or greater stenosis was present in both the circumflex and left anterior descending coronary arteries, a defect was seen in the artery with the greater narrowing.

Clinical applications: The clinical utility of the dual isotope macroaggregated albumin technique is uncertain and requires further study. At present, the technique appears potentially useful in two situations. First, it may ascertain the hemodynamic importance of a stenosis of questionable significance by arteriography. Coronary arteriographic–post mortem correlations have shown that the anatomic severity of stenoses is commonly underestimated by arteriography.[24] Additionally, the failure to identify significant lesions has been implicated in surgical mortality.[25] Second, the technique may help identify viable myocardium contiguous with old or recent myocardial infarction; that is, it may show hyperemic image defects contiguous with the resting defects. This information may help predict the need for revascularization to such segments. Kay et al.,[26] for example, have shown that revascularization with improved myocardial performance may be accomplished in regions of old infarction even though preoperative indexes of graftability were obscured by the associated infarction.

Although the results of this study are preliminary, they demonstrate that the dual isotope technique is capable of adding supplemental direct physiologic information to the anatomic information obtained by arteriography.

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Detection of Acute Myocardial Infarction by Technetium-99m Polyphosphate

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Experimental work has shown that technetium-99m (^{99m}Tc) pyrophosphate accumulates in recently infarcted myocardium and can be detected by external imaging techniques. Twenty-two ^{99m}Tc polyphosphate myocardial studies were performed in 17 patients (in 3 after cardiac surgery) 3 to 20 days after myocardial infarction. Seventeen myocardial studies were performed in 17 control patients (in 6 after cardiac surgery). Twenty millicuries of ^{99m}Tc polyphosphate was injected intravenously 60 to 120 minutes prior to gamma camera imaging in several views. Myocardial images were processed by the Gamma-11 computer system using standardized background subtraction and contrast enhancement. Results of 16 myocardial studies performed 4 to 20 days after transmural myocardial infarction in 12 patients were positive in 13 instances and questionable in 1. The location of the myocardial infarction by imaging corresponded to location by standard electrocardiographic criteria in 8 of the 10 patients with positive findings. In five patients with nontransmural myocardial infarction, results of myocardial imaging were positive in two, questionable in one and normal in one. In one patient with questionable findings results were normal when imaging was repeated 16 days after nontransmural myocardial infarction. Results of 17 control myocardial imaging studies were normal in 16 and questionable in 1. Therefore, ^{99m}Tc polyphosphate myocardial imaging appears promising in the detection and location of transmural myocardial infarction. Its accuracy in detecting nontransmural myocardial infarction may be increased with greater experience and development of sophisticated digital analysis techniques. The method may prove useful in clinical situations such as cardiac surgery in which standard diagnostic aids are difficult to interpret.

The diagnosis of myocardial infarction by standard electrocardiographic and serum enzyme criteria has proved difficult in many clinical situations. Patients with a history of severe typical or atypical chest pain can pose difficult diagnostic problems in the following settings: S-T segment changes or T wave inversion without serum enzyme elevation, previous transmural myocardial infarction with extension, serum enzyme elevation without Q waves and myocardial infarction in the presence of left bundle branch block or after cardiac surgery. Numerous radiopharmaceutical agents have been proposed to identify infarcted myocardial tissue by external imaging techniques after peripheral injection of the radionuclide. Poor availability of these radionuclides, technical difficulties or inability to obtain a positive image of the myocardial infarction has limited the widespread clinical acceptance of previously described techniques. Bonte[1] and Meyer[2] and their co-workers have shown that technetium-99m (^{99m}Tc) pyrophosphate accumulates in recently infarcted myocardium and can be imaged by a gamma camera. This paper describes the results of 39 ^{99m}Tc polyphosphate myocardial imaging studies in 34 patients.

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Methods and Materials

Thirty-four patients had myocardial images recorded between March and May, 1974. All studies were performed with use of a Conuclear gamma camera with a low energy parallel hole collimator. Imaging was performed 60 to 120 minutes after intravenous injection of 20 millicuries (mc) of ^{99m}Tc polyphosphate (New England Nuclear Corporation) in the coronary care unit or in the general wards. Patients were then transferred to the Department of Nuclear Medicine under medical supervision. ^{99m}Tc polyphosphate has a calculated total body radiation dose of 0.01 rads/mc and a half-life of 6 hours. The total dose of phosphate administered per study was 10 mg. Images of 500,000 counts were recorded on Polaroid® film in 30°, 45° and 60° left anterior oblique, left lateral and 45° right anterior oblique views over approximately 30 seconds. Data were also collected on a Gamma-11 computer system (Digital Equipment Corporation). To determine background activity in normal soft tissue and blood a region of interest was defined in the anterior mediastinum at the level of the second costosternal junction directly behind the sternum (Fig. 1). The average number of counts per matrix cell of this area was subtracted from those of all other cells in the image and the resulting image with contrast enhancement* was recorded on Polaroid film. A histogram was constructed for each view by taking a horizontal slice through the mid-portion of the myocardial mass in normal images or through areas of increased myocardial uptake in abnormal images. Anatomic landmarks were readily identifiable in most images but, when necessary, a point source of ^{99m}Tc was placed at the apex, sternal angle and mid-thoracic spine to define these landmarks.

Patient Groups

Control group: Seventeen studies were performed in 17 control patients who had not had a recent myocardial infarction. Four had had an infarction at least 3 months previously; one had had acute coronary insufficiency without infarction 3 years before the study. Six patients were studied 6 to 12 days after cardiac surgery, three after aortocoronary bypass and three after mitral commissurotomy. The remaining control patients had cardiomyopathy, arrhythmias or valvular heart disease.

Patients with myocardial infarction: Seventeen patients were studied 3 to 20 days after acute myocardial infarction. Sixteen studies were performed in 12 patients with transmural myocardial infarction as defined by the appearance of new Q waves, evolving S-T segment and T wave changes and rises in serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and hydroxybutyric dehydrogenase (HBDH) levels. Two patients of this group had a transmural myocardial infarction after aortocoronary bypass surgery; in the remaining 10 cases the infarction was unrelated to surgery. Six studies were performed in five patients with nontransmural myocardial infarction defined by the presence of S-T and T wave changes and rises in SGOT, LDH and HBDH levels without new Q waves. One of these patients had a nontransmural myocardial infarction after aortic valve replacement; in the other four, the myocardial infarction was not related to surgery.

*Standard PDP 11/40 contrast enhancement program. After background subtraction the range of density from 0 to maximum was distributed over the remaining range of counts.

TABLE I

Results of ^{99m}Tc Polyphosphate Myocardial Images in 17 Control Patients

Diagnosis	Result of Image		
	Negative	Questionable	Positive
Post-cardiac surgery	5	1	0
Old myocardial infarction	5	0	0
Cardiomyopathy	2	0	0
Arrhythmia	2	0	0
Valvular heart disease	2	0	0
Total patients	16	1	0

TABLE II

Results of ^{99m}Tc Polyphosphate Myocardial Images in 17 Patients with Myocardial Infarction

Days After Infarction (no.)	Result of Image		
	Negative	Questionable	Positive
A. Transmural Myocardial Infarction (12 patients)			
0–7	1*	0	9
8–14	1*	1	3
15–21	0	0	1
Total images	2	1	13
B. Nontransmural Myocardial Infarction (5 patients)			
0–7	1	2	2
8–14	0	0	0
15–21	1	0	0
Total images	2	2	2

* Same postoperative patient.

Results

All images were interpreted independently and blindly by three observers as positive, questionable or negative. Positive myocardial images had areas of increased myocardial activity in at least two views and an abnormal peak of activity on the histogram in the same area. Questionable myocardial images had in one view areas of some increase in myocardial uptake that could not be visualized in any other view and that had a low peak on the histogram. Negative myocardial images had no areas of increased myocardial uptake in any view.

Control Group

The results of the 17 control myocardial studies are summarized in Table I; findings were negative in 16 and questionable in 1 patient studied 6 days after closed mitral commissurotomy. This patient had S-T segment elevation in the precordial leads postoperatively, but there were no evolutionary changes of myocardial infarction on subsequent electrocardiograms; serum enzyme studies were not available. Figures 1 and 2 are representative control images.

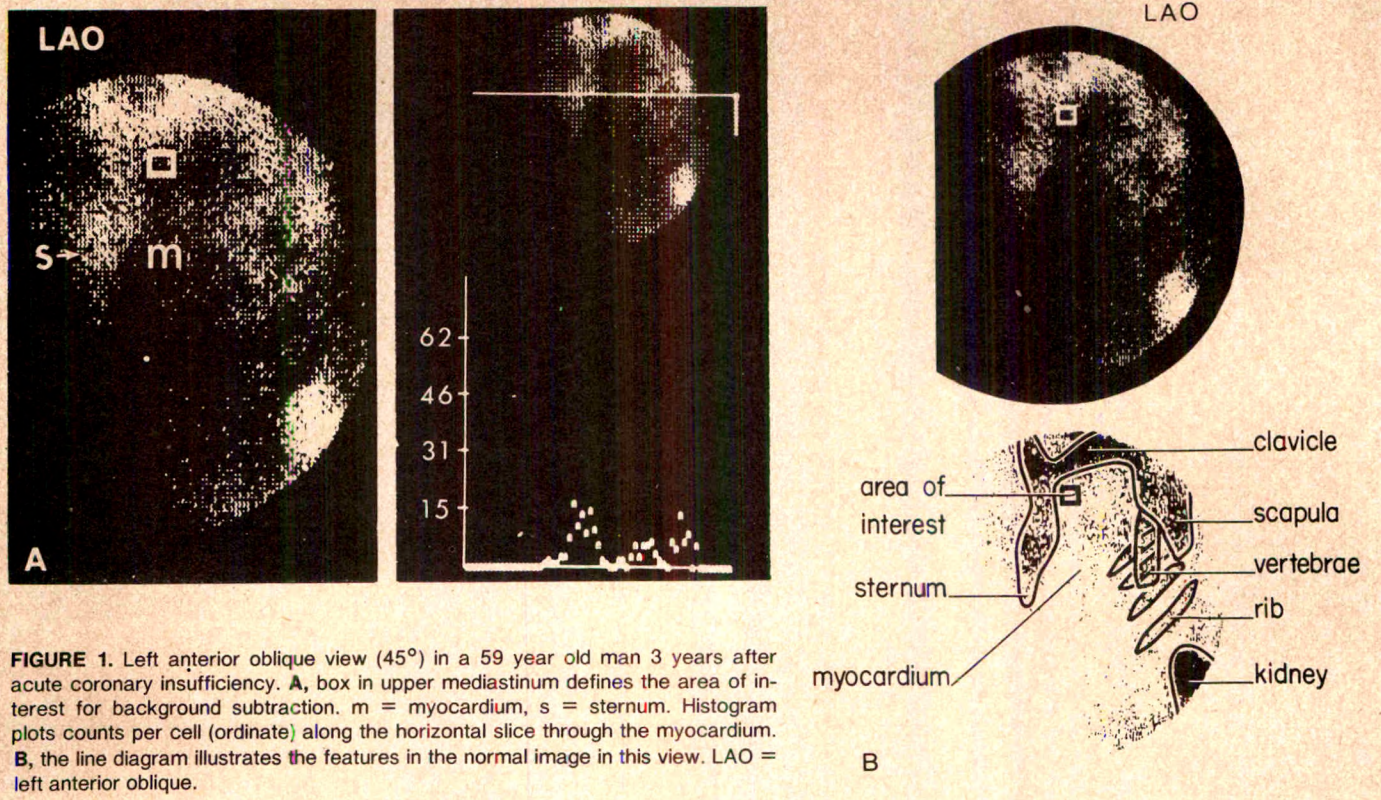


FIGURE 1. Left anterior oblique view (45°) in a 59 year old man 3 years after acute coronary insufficiency. **A,** box in upper mediastinum defines the area of interest for background subtraction. m = myocardium, s = sternum. Histogram plots counts per cell (ordinate) along the horizontal slice through the myocardium. **B,** the line diagram illustrates the features in the normal image in this view. LAO = left anterior oblique.

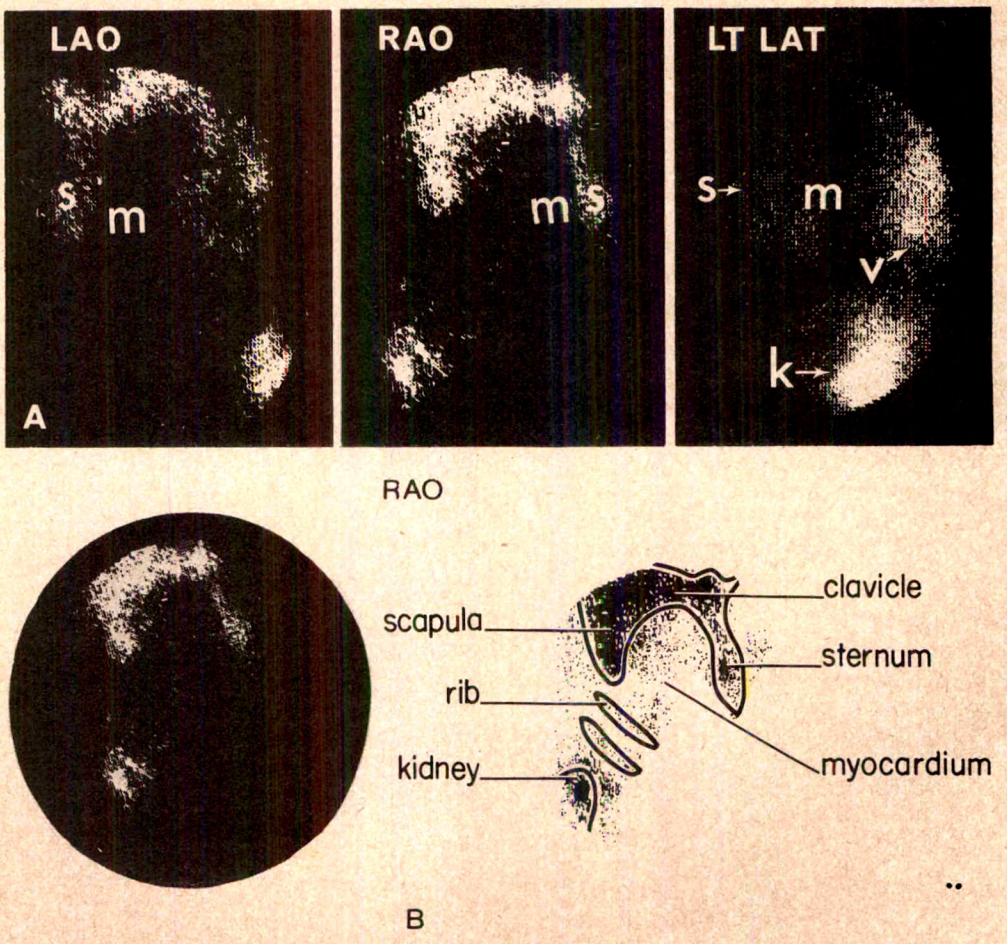


FIGURE 2. A, left anterior oblique (LAO), right anterior oblique (RAO) and left lateral (LT LAT) views in the same patient as in Figure 1. No increase in myocardial (m) uptake is seen behind the sternum (s). Kidney (k) and vertebrae (v) are indicated in the left lateral view. **B,** the line diagram illustrates the normal image in the right anterior oblique view.

Patients with Myocardial Infarction

The results of ^{99m}Tc polyphosphate myocardial images in 17 patients with myocardial infarction are summarized in Table II.

Transmural myocardial infarctions: Of the 16 studies recorded in 12 patients with transmural myocardial infarction, 13 (10 patients) were positive, 1 was questionable and 2 (1 patient) were negative. Figure 3 depicts a positive study in a 64 year old man with an inferior myocardial infarction. Figure 4 illustrates findings in a 53 year old man with anterior myocardial infarction. Results of 9 of 10 studies recorded in nine patients within 1 week of a transmural myocardial infarction were positive. One patient had positive images 3 and 7 days, respectively, after myocardial infarction. The one negative study in the 1st week was recorded in a patient 5 days after a perioperative myocardial infarction. Results were again negative when the study was repeated 12 days postoperatively. Of the other four studies recorded in the 2nd week after a transmural myocardial infarction, results were positive in three and questionable in one. One of these positive studies was recorded 8 days after infarction in a patient with a previous positive study four days after infarction. The other two positive studies in the 2nd week were recorded in two patients who first underwent imaging 9 and 14 days, respectively, after myocardial infarction. The questionable study was recorded in a patient in whom imaging was first performed 12 days after a nonsurgical myocardial infarction. Results of the one study recorded in the 3rd week (20 days) after transmural

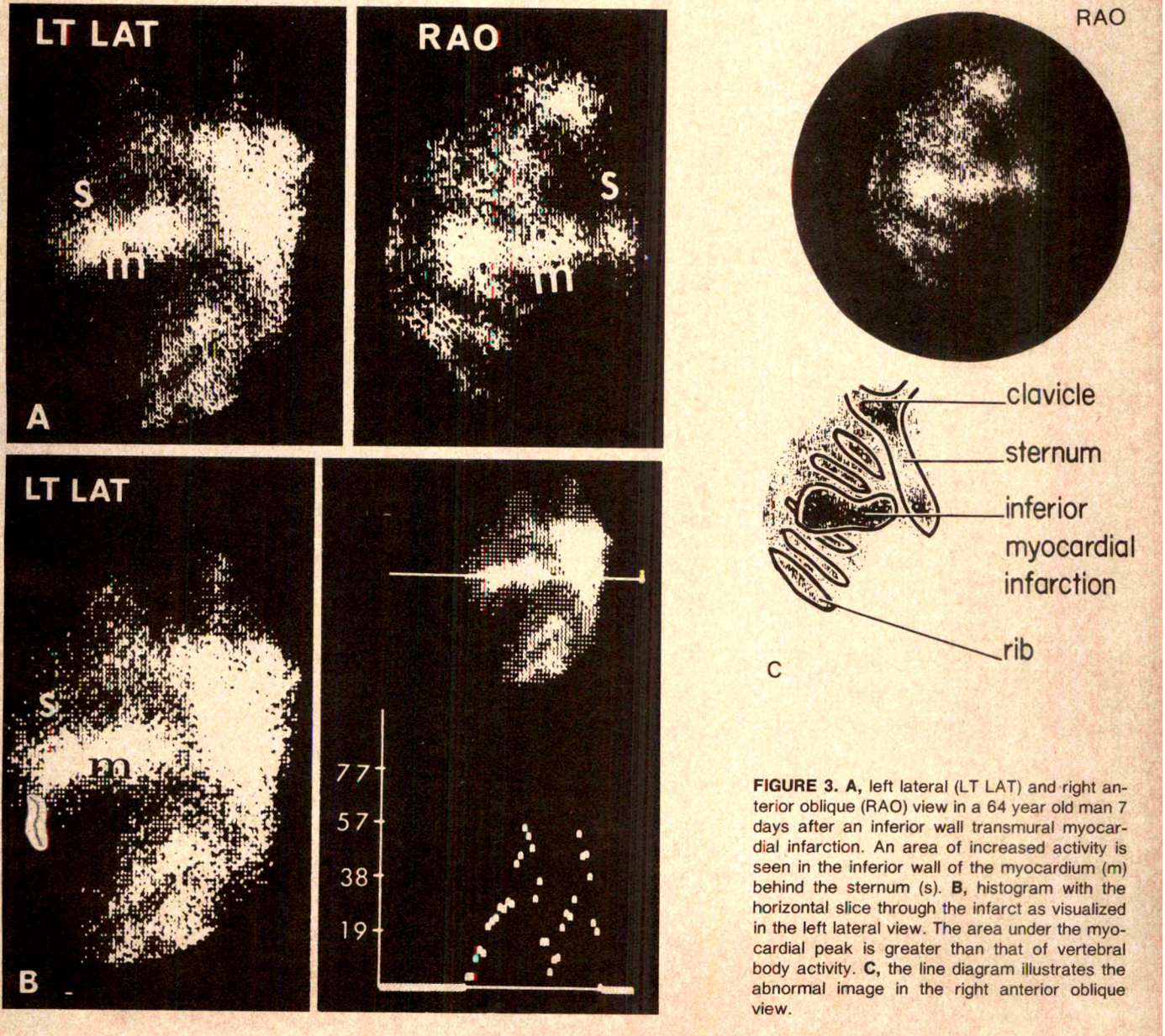


FIGURE 3. A, left lateral (LT LAT) and right anterior oblique (RAO) view in a 64 year old man 7 days after an inferior wall transmural myocardial infarction. An area of increased activity is seen in the inferior wall of the myocardium (m) behind the sternum (s). **B,** histogram with the horizontal slice through the infarct as visualized in the left lateral view. The area under the myocardial peak is greater than that of vertebral body activity. **C,** the line diagram illustrates the abnormal image in the right anterior oblique view.

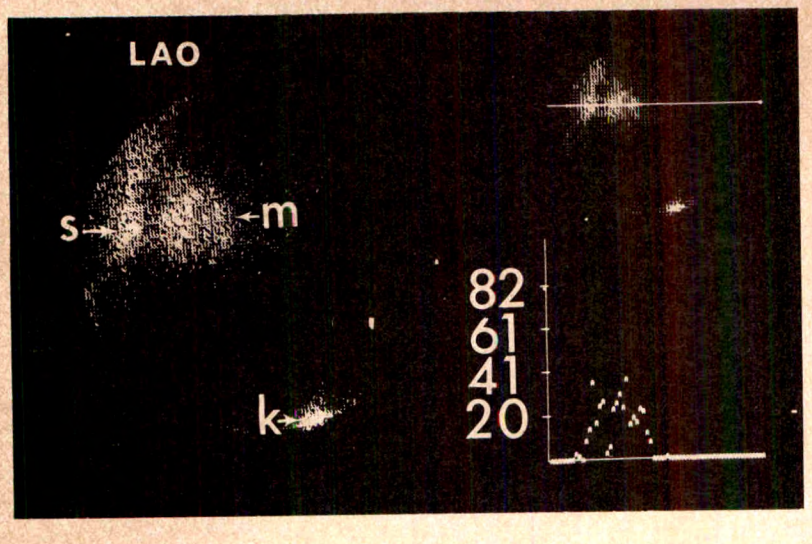
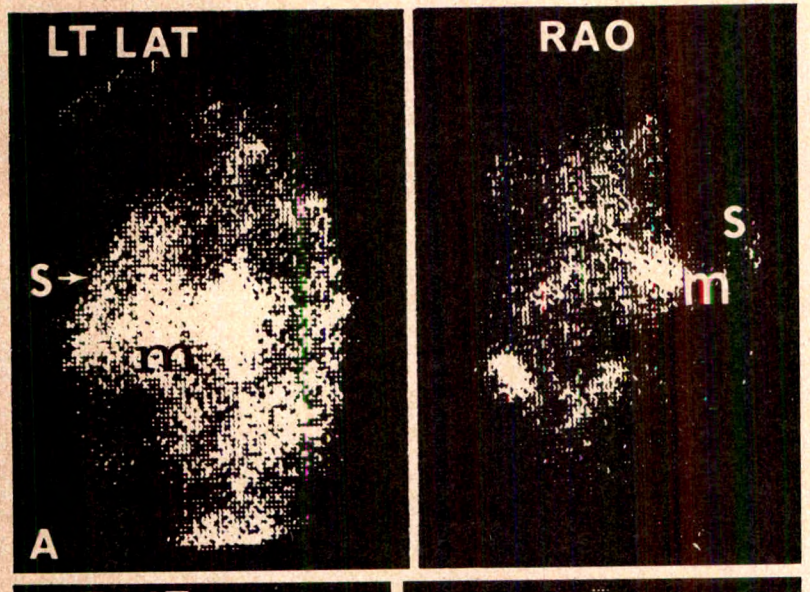
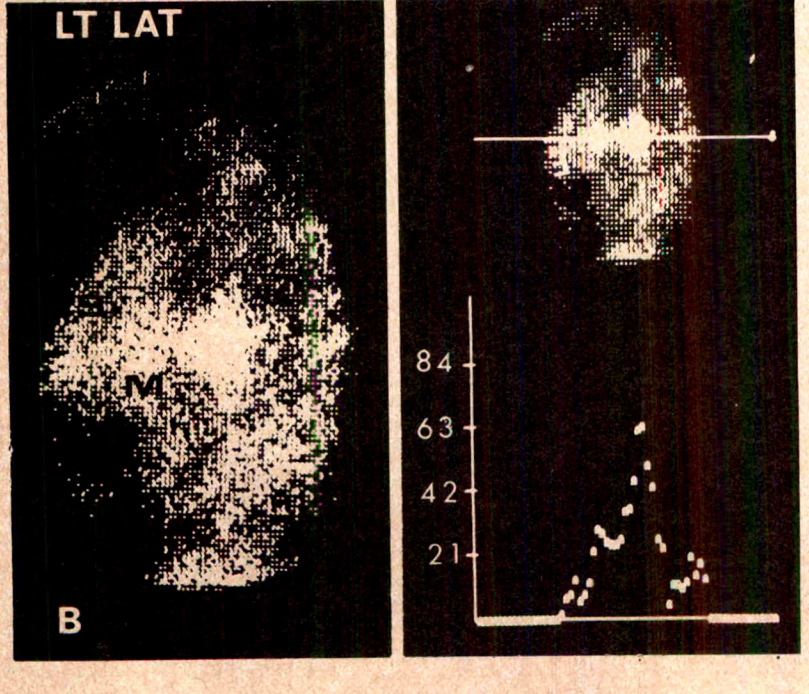


FIGURE 4. Left anterior oblique (LAO) view, with histogram, in a 53 year old man 20 days after a transmural anterior myocardial infarction. An area of increased activity is seen directly behind the sternum (s) in the anterior wall of the myocardium (m). The upper pole of the kidney (k) is visualized. The histogram demonstrates the abnormal myocardial peak behind the sternum.





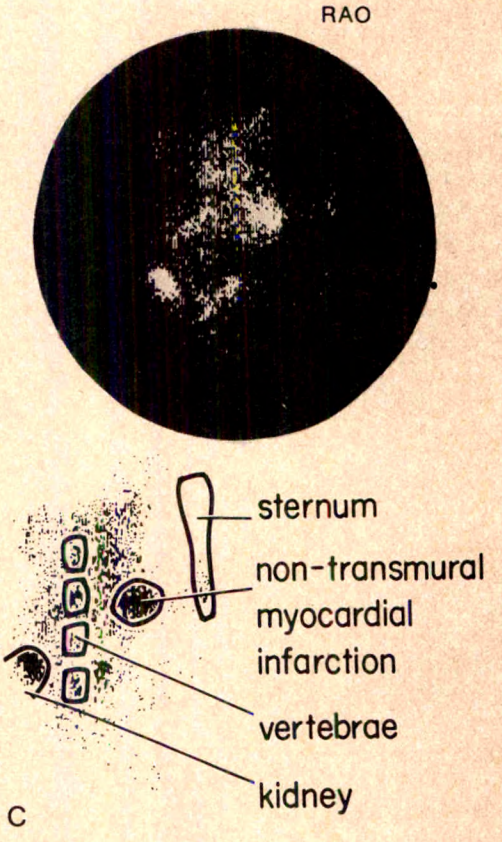


FIGURE 5. A, left lateral (LT LAT) and right anterior oblique (RAO) views in a 42 year old woman 3 days after a nontransmural anterolateral myocardial infarction. An area of increased activity is seen in the myocardium (m) behind the sternum (s). **B,** histogram of the hourglass-shaped area of increased activity demonstrating the abnormal myocardial peaks. **C,** the line diagram illustrates the abnormal image in the right anterior oblique view.

myocardial infarction were positive. This patient had a previously positive study recorded the 1st week after infarction.

Location of myocardial infarction: The location of the transmural myocardial infarction by imaging corresponded to location by standard electrocardiographic criteria in 8 of the 10 patients with positive findings. One anterior and one inferior infarction could not be accurately located by imaging. By electrocardiographic criteria, five myocardial infarctions were anterior, three were inferior, one was true posterior and one was both anterior and inferior.

Nontransmural myocardial infarction: Six myocardial studies were recorded in five patients with nontransmural myocardial infarction. Results were positive in two, questionable in two and negative in two. Figure 5 demonstrates one of the positive studies. The two positive studies were recorded in two patients, 3 and 4 days, respectively, after a myocardial infarction. One of the two questionable studies was obtained in a patient 5 days after a myocardial infarction, the other was recorded in a patient 7 days after a myocardial infarction precipitated by aortic valve replacement; findings were negative in this patient when the study was repeated 16 days after surgery. The one negative study recorded in the 1st week was obtained in a patient 3 days after a nontransmural myocardial infarction.

Discussion

Negative vs. positive myocardial imaging: Many radiopharmaceutical agents have been used to detect myocardial ischemia and infarction.[3–15] Most of the techniques using these substances depend on failure of the ischemic or scarred myocardium to take up the radionuclide, thereby producing a negative image.[3–11] Radionuclides producing a negative image include cesium-129, cesium-131, cesium-134, rubidium-81, nitrogen-13, potassium-42, potassium-43 and radiolabeled fatty acids. The disadvantages of these techniques include failure to distinguish recent from old myocardial infarction and poor physical characteristics or poor availability of the radionuclides. The other major disadvantage of a negative image is the loss of sensitivity from superimposition of "cold" over normal areas of myocardium as a result of the spherical geometry of the left ventricle. Technetium-99m tetracycline and mercury compounds have been utilized for positive imaging of myocardial infarction[11–15]; however, they are not currently in widespread use because of difficulties in production and biological instability of ^{99m}Tc tetracycline and renal toxicity of the mercury radiopharmaceutical agents.

^{99m}Tc pyrophosphate has been shown to accumulate in recently infarcted myocardium.[1,2] This agent is used in many hospitals as a bone scanning agent and is readily available. The radiation dose and phosphate load are well within safe limits. Polyphosphate was used in this study because it is our routine bone scanning agent. Our patients have experienced no morbidity or mortality as a result of myocardial imaging and neither has been reported with the widespread use of ^{99m}Tc polyphosphate in bone scanning over several years. Twenty mc of ^{99m}Tc polyphosphate was selected to permit rapid imaging. From our experience the optimal imaging time appears to be between 60 and 120 minutes after injection.

Mechanism of localization of ^{99m}Tc polyphosphate in infarcted myocardium: Experimental documentation of the mechanism of localization of ^{99m}Tc polyphosphate is lacking. Bonte[1] and Meyer[2] and their co-workers have suggested that phosphate accumulates in mitochondria of infarcted cells in association with increased mitochondrial uptake of calcium ion. Other possible mechanisms include binding of phosphate to damaged cell membranes, uptake in other cytoplasmic or nuclear organelles, or binding to leukocytes invading the infarcted area. Technetium-99m polyphosphate myocardial imaging can accurately diagnose transmural myocardial infarction. Imaging of nontransmural myocardial infarction was less accurate in our small group of five patients, but results may improve with greater experience. Our data indicate that positive images may be achieved up to 20 days after myocardial infarction, although the sensitivity of detection of the method decreased with time in one patient with serial studies. In addition, imaging studies were normal in all four control patients whose myocardial infarction occurred more than 3 months before study. This method shows promise as a means of distinguishing recent from remote myocardial infarction.

The interval between myocardial infarction and positive images in our study is longer than that reported by Meyer et al.[2], but the number of patients in each study is small. The duration of this interval may well be quite variable and requires further study.

Perioperative myocardial infarction: Clinical diagnosis of myocardial infarction sustained during cardiac surgery may be difficult. Two patients with positive images had perioperative myocardial infarction as assessed by clinical data. One patient who had a transmural myocardial infarction and a positive myocardial image after aortocoronary bypass surgery underwent graft arteriography that demonstrated an occluded graft supplying the area of myocardium with increased uptake of ^{99m}Tc polyphosphate. The other patient with a suspected nontransmural myocardial infarction had a questionable study 7 days after aortic valve replacement and another that was normal 9 days later. These data suggest that ^{99m}Tc polyphosphate imaging may increase the accuracy of diagnosis of perioperative myocardial infarction.

Location of infarction: ^{99m}Tc polyphosphate imaging can also indicate the location of a recent myocardial infarction in a high precentage of patients. The usefulness of this is apparent in patients with suspected extension of myocardial infarction or those with left bundle branch block by electrocardiogram.

Future improvements in technique: It is not known whether ^{99m}Tc polyphosphate is taken up by ischemic tissue that has not yet undergone infarction.

Further work is ongoing to clarify this important point. Further investigation is also underway to develop techniques to improve resolution. Physiologic gating of respiratory and cardiac cycle and computer manipulation of the data to subtract overlying rib activity hold promise. Stokely et al.[16] have described a digital band reject filter to subtract overlying rib activity, and we have had promising preliminary results using their algorithm.

In summary, use of ^{99m}Tc polyphosphate shows promise in detecting the presence and location of recent myocardial infarctions. Further investigation is required to determine the mechanism of localization of ^{99m}Tc polyphosphate in infarcted myocardium, to define further the limits of sensitivity of infarct detection and to develop techniques to improve resolution and data manipulation.

Acknowledgment

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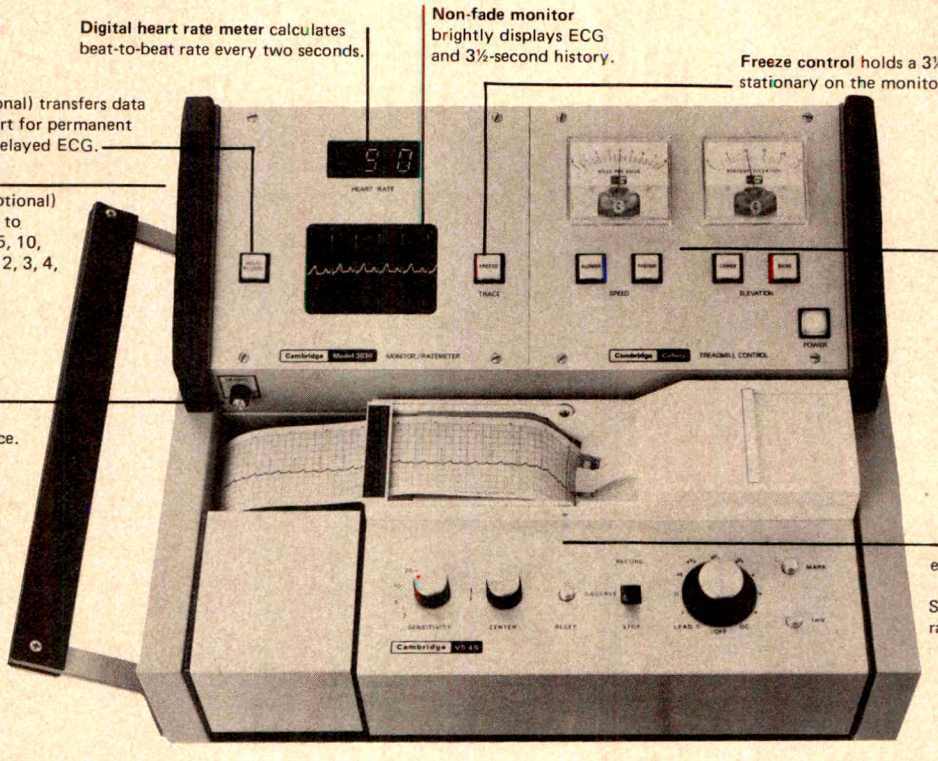

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Principles of oral anticoagulation

Practical Considerations

Identifying your patient at risk of thromboembolic complications

While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

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For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

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Therapeutic principles put into practice

COUMADIN®
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BRIEF SUMMARY

INDICATIONS: COUMADIN (crystalline sodium warfarin) is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

CONTRAINDICATIONS: Hemorrhagic blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms—cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities,** or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional block anesthesia.

WARNINGS: Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risk of hemorrhage due to anticoagulants is weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with increased risk of hemorrhage: **Pregnancy**—oral anticoagulants pass through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage *in utero*, even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. **Lactation**—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Severe trauma** of head, bones or muscles associated with extreme raw surfaces. **Surgery** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS: Periodic determination of prothrombin time is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN (crystalline sodium warfarin) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN (crystalline sodium warfarin) underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

ADVERSE REACTIONS: Potential side effects of COUMADIN (crystalline sodium warfarin) include: 1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.) Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc. 2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

TREATMENT FOR OVERDOSAGE: Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN (crystalline sodium warfarin) may suffice; and if necessary, small doses of vitamin K_1 (Mephyton®*) orally, 2.5 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 (AquaMephyton®*) in doses of 10 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.) Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN (crystalline sodium warfarin) administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level is readily obtained.

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For complete prescribing information, including dosage and laboratory control, see package circular.

SUPPLIED: Tablets: COUMADIN (crystalline sodium warfarin) for oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100. **Injection:** Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units, 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thimerosal, 0.3 mg. pH is adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Injection.

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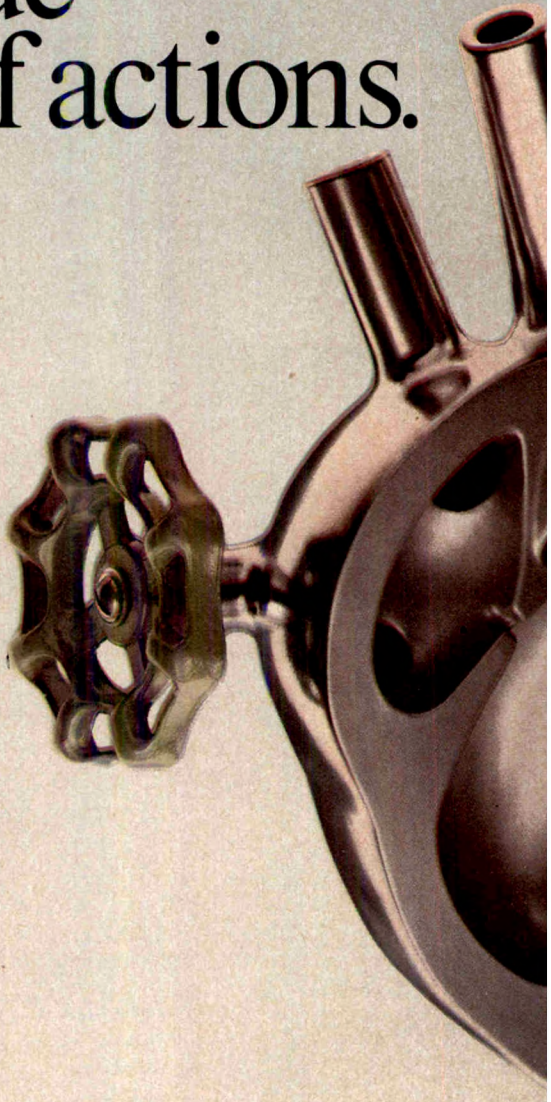

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Increased urine output

Intropin significantly increases urine flow. This is in contrast to most other sympathomimetic amines, which usually cause little or no significant increase in urine output.

This increased urine output is due to increases in glomerular filtration rate and renal blood flow and is accompanied by increased sodium excretion. Intropin may also increase urine flow in patients whose urine output is within normal limits and may promote diuresis usually with no decrease in osmolality.

At doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage.

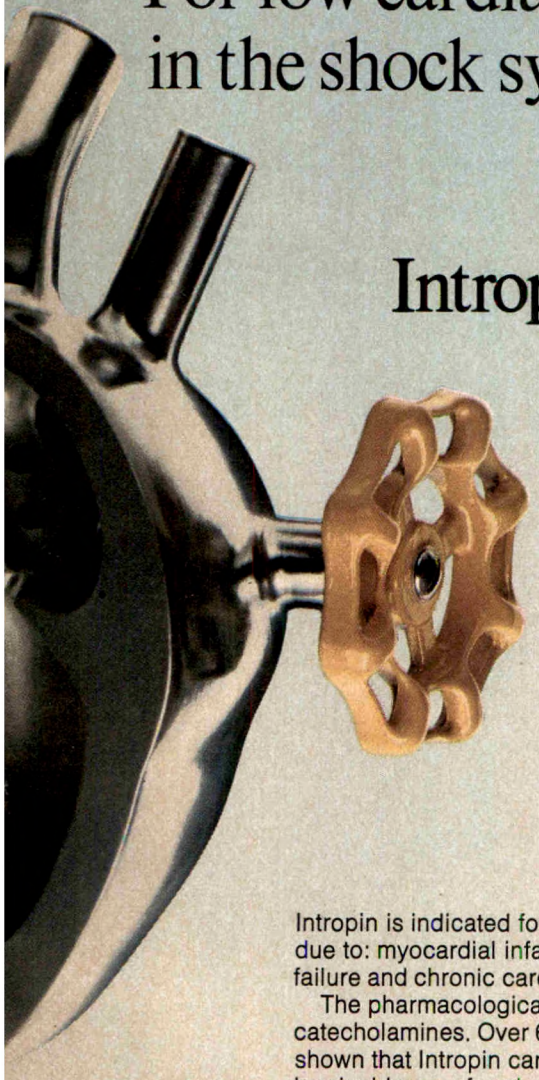
Increased cardiac output

Intropin acts predominantly on the beta receptors of the heart to substantially increase contractility, stroke volume and cardiac output, as confirmed by invasive technique.

Increased blood pressure

Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of Intropin. Prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer Intropin as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

For low cardiac output and hypoperfusion in the shock syndrome.



Intropin usually will not turn on:

A substantial increase in tachyarrhythmias

One investigator reported less than a 3% incidence of tachyarrhythmias in clinical trials of 270 patients. The tachyarrhythmias which occurred were easily managed.

Excessive myocardial oxygen consumption

Intropin produces less increase in myocardial oxygen consumption than isoproterenol. During administration of Intropin, the myocardial oxygen supply/demand ratio has usually remained stable. Intropin appears to meet additional myocardial oxygen requirements by increasing coronary flow.

Increased total peripheral resistance

Administration of Intropin, at low and intermediate dosages, generally does not increase total peripheral vascular resistance. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases.

Intropin is indicated for the correction of hemodynamic imbalances in the shock syndrome due to: myocardial infarction, trauma, endotoxic septicemia, open heart surgery, renal failure and chronic cardiac decompensation as in congestive failure.

The pharmacological actions of Intropin appear to differ significantly from other catecholamines. Over 6 years of clinical trials at more than 30 teaching hospitals have shown that Intropin can increase cardiac output, vital organ perfusion and renal flow with a low incidence of undesirable effects.

Patients most likely to respond adequately to Intropin are those in whom urine flow, myocardial function and blood pressure have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and Intropin, the better the prognosis. Survival rates are considerably improved when Intropin therapy is initiated within 4 hours of onset of symptoms.

As with all potent drugs, Intropin must be administered under close medical supervision. It is administered only by I.V. drip after dilution in a suitable I.V. solution.

Serious undesirable effects seldom occur

In multiclinic studies, adverse reactions necessitated discontinuation of Intropin therapy in only 11 (2%) of 526 patients.

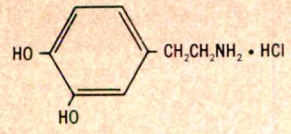
Before prescribing, see complete product information on the following page.

ARNAR-STONE LABORATORIES, INC.

INTROPIN® (dopamine HCl)

5 ml. AMPUL / FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3,4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do NOT add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Although in clinical trials inadvertent subcutaneous infiltration did not produce any evidence of necrosis, the usual precautions should be taken to avoid extravasation.

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

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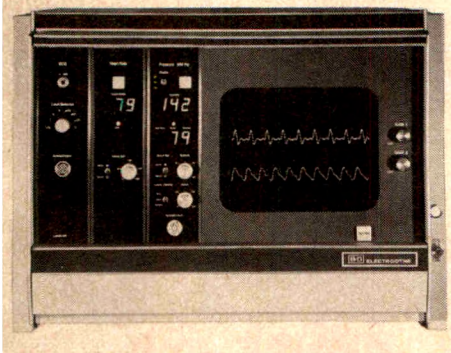

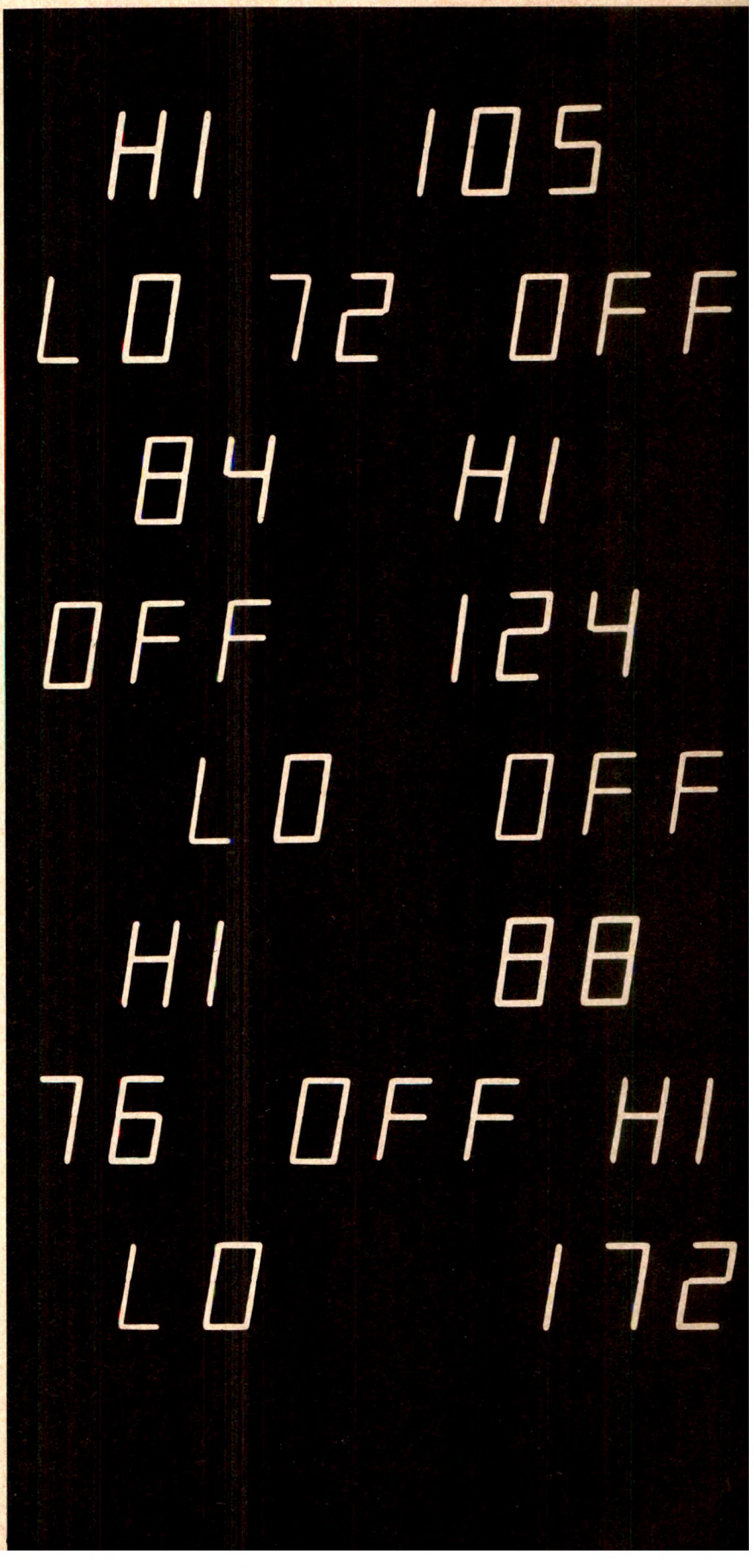

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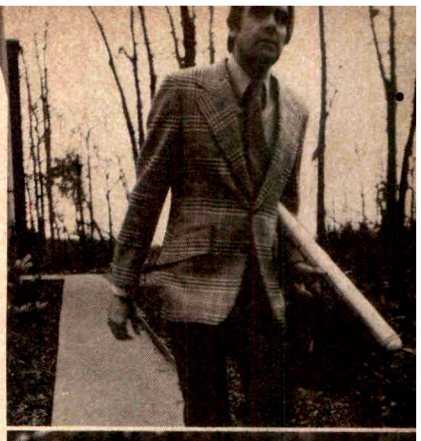
AN ANTIHYPERTENSIVE FROM AYERST

the "healthy" hypertensive



It may be years before he experiences a single symptom of hypertension. But left untreated, even mild to moderate elevations of blood pressure may quietly strip years from an otherwise healthy and active life. Early control with DIUCARDIN may help forestall damage to healthy target organs.

DIUCARDIN provides approximately the same diuretic potency as hydrochlorothiazide at maximal therapeutic dosage. With DIUCARDIN, the onset of diuresis is gradual and may be maintained for twelve hours or more with a single dose.[1,2] The antihypertensive effect of DIUCARDIN is usually maintained in long term use. For many patients on DIUCARDIN, a convenient once-a-day dosage may suffice.

DIUCARDIN provides a good beginning for many hypertensive patients. DIUCARDIN 50 mg. Tablets. For mild to moderate hypertension and adjunctive therapy for many types of edema.

Ayerst®

controlled early on

Diucardin® TABLETS

(hydroflumethiazide)

diuretic/antihypertensive

(See prescribing information on next page.)

For the "healthy" hypertensive, early control with

Diucardin® TABLETS (hydroflumethiazide)

diuretic/antihypertensive

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

The mechanism(s) of the antihypertensive action of the thiazides has not been elucidated.

INDICATIONS: **Hypertension:** DIUCARDIN alone may provide adequate control in mild or moderate hypertension. In severe hypertension or in cases of mild or moderate hypertension which do not respond adequately, DIUCARDIN may be used in conjunction with other antihypertensive agents.

DIUCARDIN alone or in conjunction with other antihypertensive agents is indicated for control of hypertension in pregnancy. (See WARNINGS)

Edema: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: **Gastrointestinal:** anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: **Usual adult dosage:** 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN—No. 702—Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.

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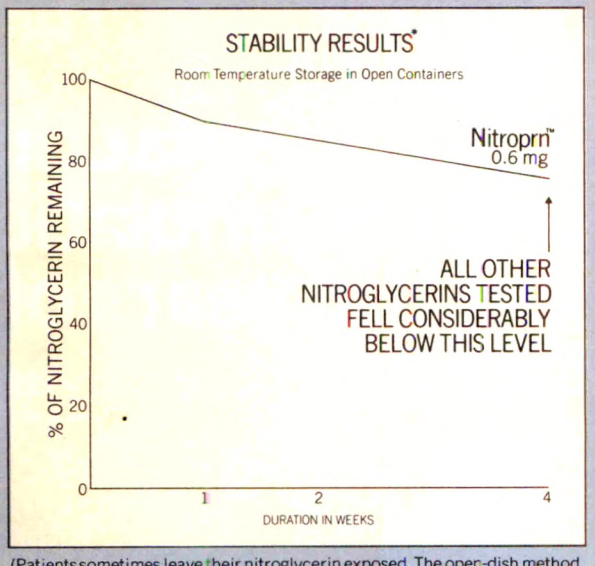

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*Methods used: The semi-automated Content Uniformity Assay based on the procedure of Fusari, S.: J. Pharm. Sci. 62:122 (1973), with modifications by the Applied Analytical Research Laboratories of Warner-Lambert Company. Data on file, Warner-Lambert Research Institute.

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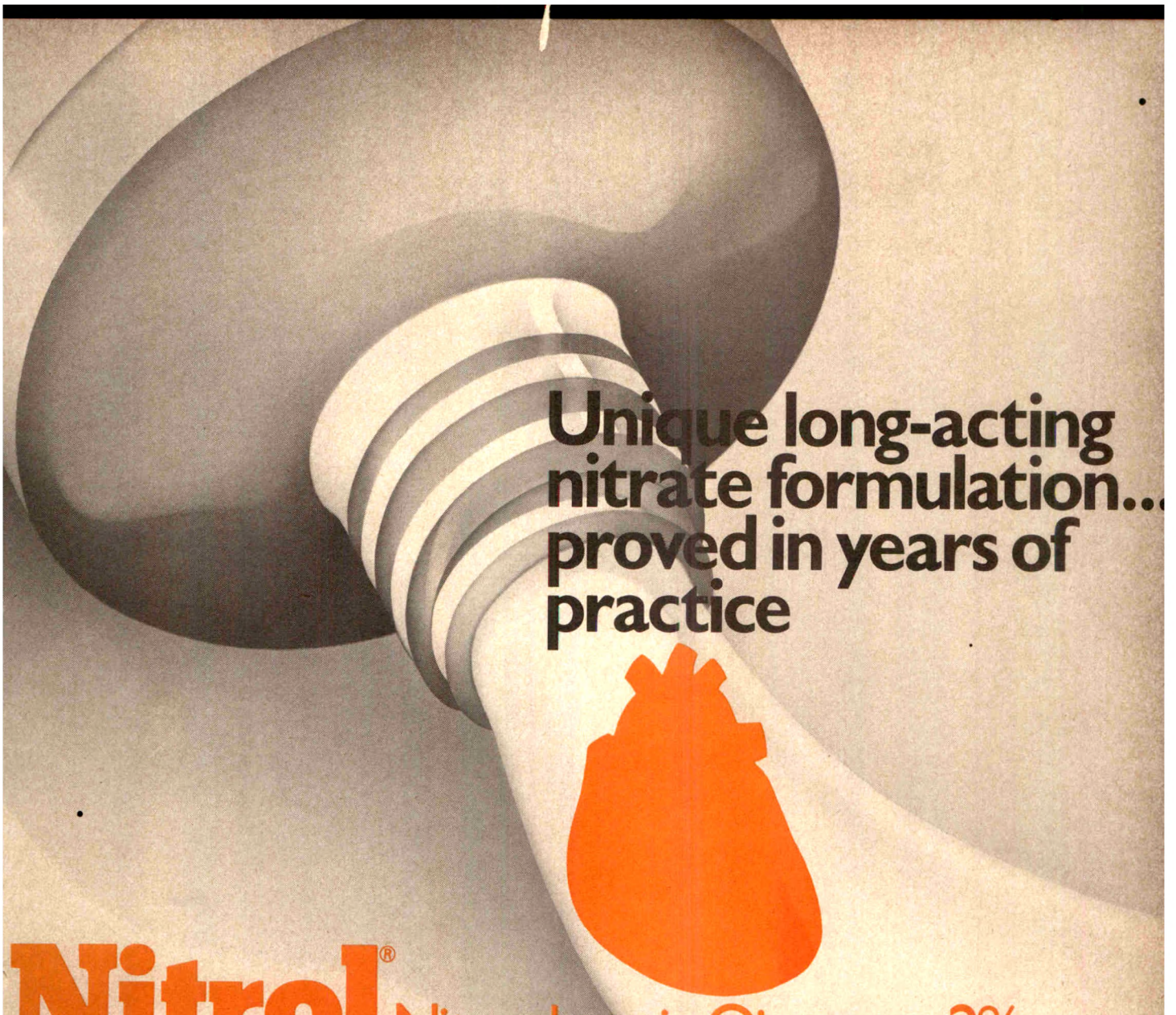

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Composition: Nitroglycerin 2% in lanolin-petrolatum base. **Administration:** From 1/2 to 2 inches applied to desired skin area by means of Appliruler supplied. Adjust to individual need, starting in lower range. **Side effects:** Headache indicates overdose. Dizziness on standing may be the result of postural hypotension. **Contraindications:** Marked anemia, increased intraocular pressure or increased intracranial pressure. **Supplied:** 1-oz. or 2-oz. tubes. **Caution:** Federal law prohibits dispensing without prescription.

References: 1. Davis, J. A., and Wiesel, B. H.: Am. J. Med. Sci. **230**:259-263 (Sept.) 1955. **2.** Reichek, N.; Goldstein, R. E.; Redwood, D. R., and Epstein, S. E.: Circulation **50**:348-352 (August) 1974.

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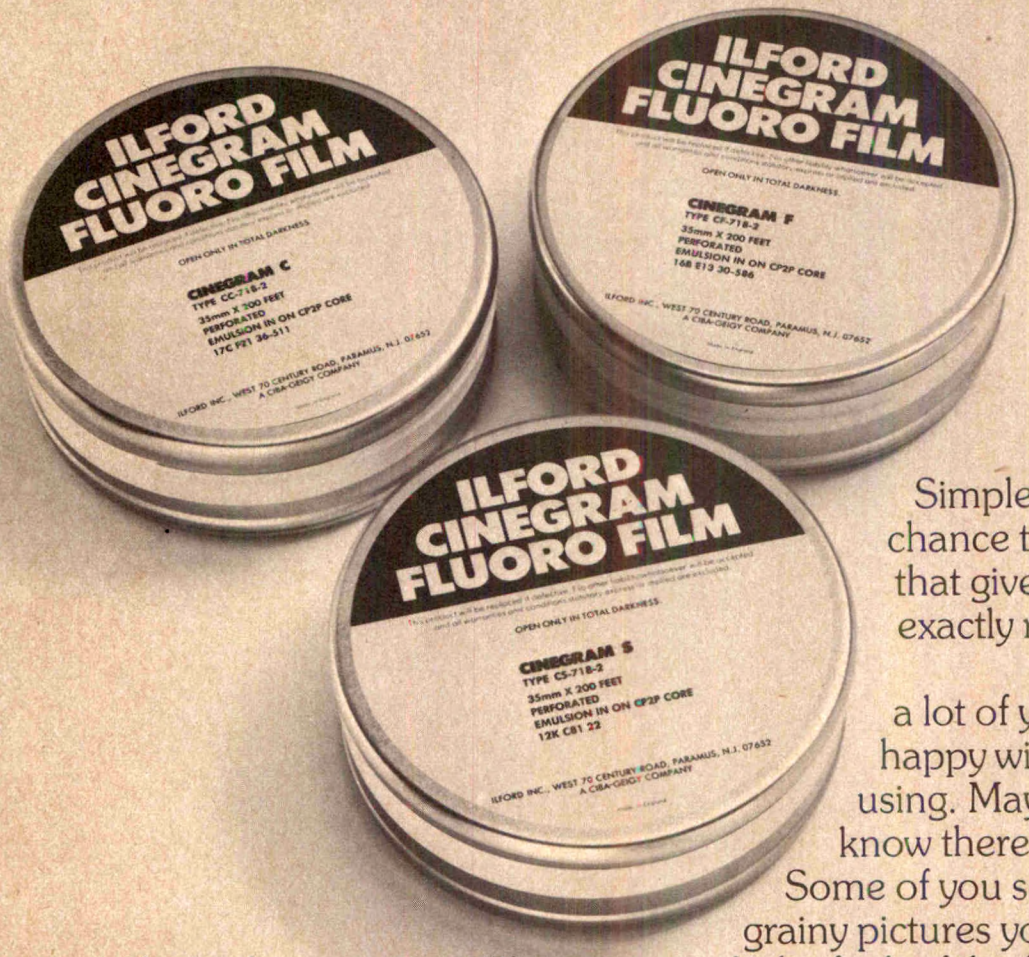

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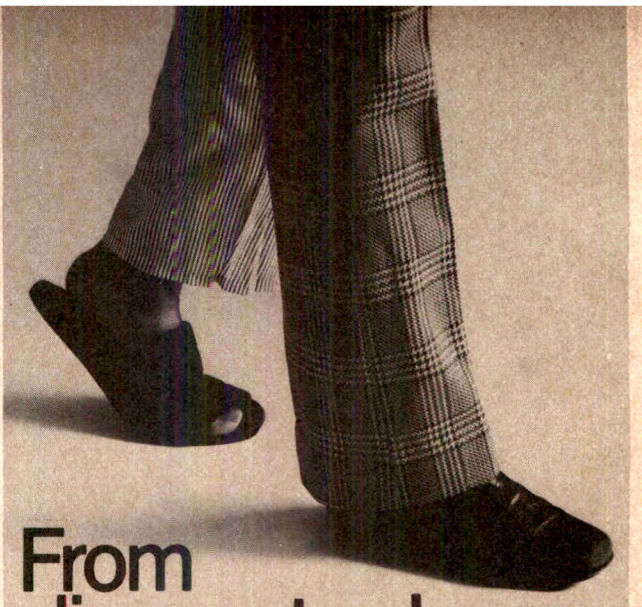

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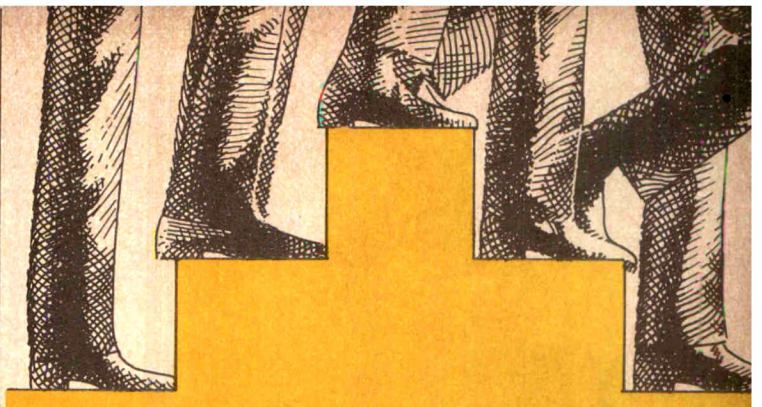

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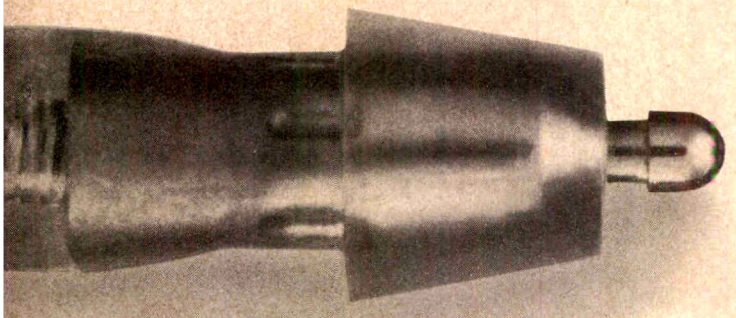

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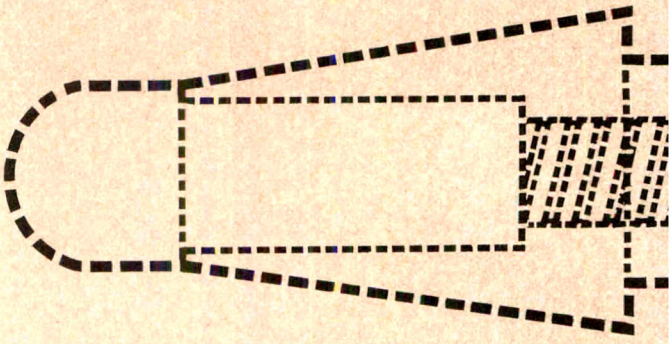

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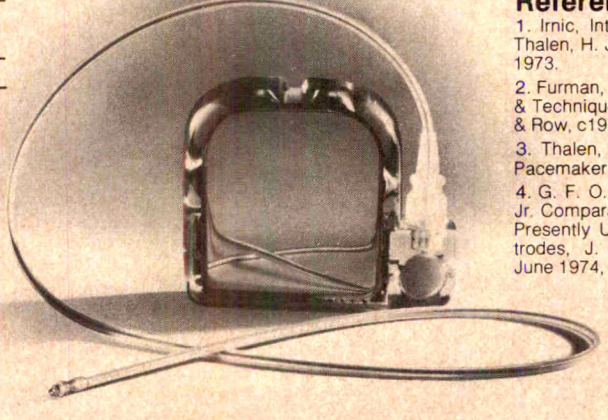

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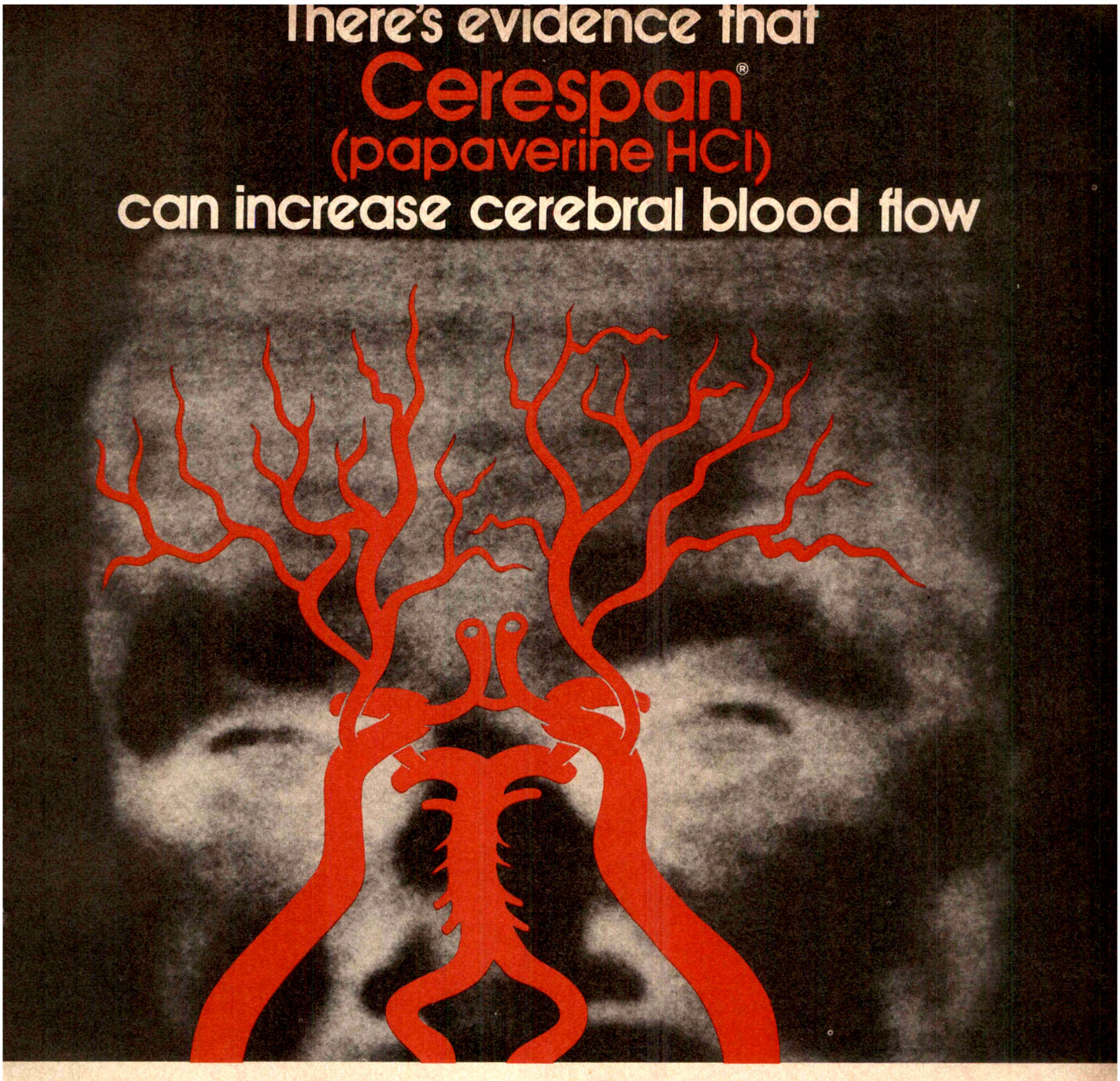

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Late Systolic Murmur of Rheumatic Mitral Insufficiency

LEONARD STEINFELD, MD, FACC
IVAN DIMICH, MD, FACC
HOWARD RAPPAPORT, MD
MURRAY BARON, MD, FACC

New York, New York

Of 184 patients with acute rheumatic fever and associated mitral insufficiency encountered during a 15 year period, 34 manifested a mid-late systolic murmur or a nonejection click, or both, during the course of follow-up.

The mid-late systolic murmur later disappeared in four patients whose condition is now considered normal. In one of the four, systolic prolapse of the mitral valve was demonstrated on an angiocardiogram obtained when the systolic murmur was present. Since disappearance of the murmur there has been no evidence of systolic prolapse on meticulous echocardiographic study of the mitral valve. In another child with angiographically demonstrated systolic prolapse of the mitral valve the systolic murmur has also disappeared, but systolic prolapse is still evident on echocardiographic study.

None of the 34 patients with a mid-late systolic murmur manifested the T wave abnormalities commonly associated with the familial variety of mitral valve prolapse.

Since Reid[1] in 1961, followed by Barlow and Pocock[2] in 1963, kindled interest in nonejection clicks and late systolic murmurs, it has become abundantly clear that these sounds, previously considered innocent, are indeed pathologic.[3,4] These abnormal sounds are generated by dysfunction of the mitral valve apparatus during systole. A variety of diseases affecting the mitral valve have been associated with clicks and late systolic murmurs,[5] and various names, of which "floppy mitral valve" [6] and "billowing sail deformity" [7] are the most descriptive, have been given to the anatomic findings. A familial disorder[8,9] observed predominantly in female subjects presenting with an apical systolic click, a late systolic murmur and T wave abnormalities has been designated a syndrome. The anatomic basis of the syndrome is late systolic prolapse of the posterior mitral leaflet.

Rheumatic mitral disease has been described as a cause of apical clicks and late systolic murmurs.[5,10–12] The frequency with which these sounds are encountered in patients with rheumatic disease is unknown and the relation of these sounds to T wave abnormalities and a ballooning mitral valve is also unknown. To shed light on these unknowns, we reviewed the clinical records of a large number of patients, each with a documented attack of acute rheumatic fever with carditis and isolated mitral insufficiency. Inclusion of these patients in a penicillin prophylaxis program afforded the opportunity for detailed observations over an extended period of time.

Case Material

In the 15 years from 1958 through 1972, 184 patients were seen at the Mount Sinai Hospital with isolated mitral insufficiency in association with a known attack of acute rheumatic fever. The diagnosis of acute rheumatic fever was established by the usually accepted modified Jones' criteria,[13] plus the presence of mitral insufficiency. One hundred sixty-five patients, 91 per-

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TABLE I

Incidence of Mid-Late Systolic Murmur

	Acute Mitral Insufficiency with Pansystolic Murmur		Mid-Late Systolic Murmur	Percent of Male, Female and Total Subjects
	no.	% of total	no.	
Male	72	39	4	5.5
Female	112	61	30	26.8
Total	184	100	34	18.5

TABLE II

Time of Appearance of Mid-Late Systolic Murmurs

Interval Between Active Onset of Rheumatic Fever and Appearance of Mid-Late Systolic Murmur	Patients (no.)
1 month	2
2–6 months	4
7–12 months	5
1–2 years	2
3–5 years	12
>5 years	9

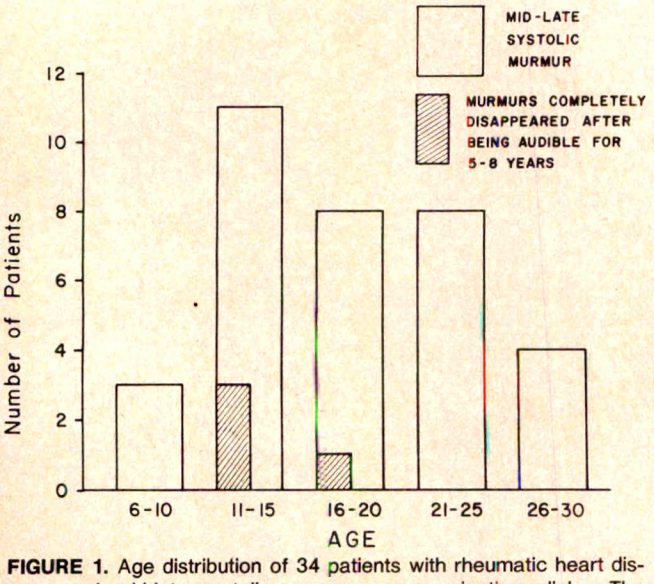

FIGURE 1. Age distribution of 34 patients with rheumatic heart disease and mid-late systolic murmurs or nonejection clicks. The hatched bars represent the four patients whose mid-late systolic murmurs have disappeared.

cent of the total group of 184, were inpatients during the acute episode. The remaining 19 patients were treated for the acute attack at another institution or at home by a family physician; a detailed medical report of the attack was available in each of these cases.

Of the 184 patients, 72 (39 percent) were male and 112 (61 percent) were female (Table I). All initially had a blowing apical pansystolic murmur or near pansystolic murmur, but 34 (18.5 percent) later manifested a late or mid-late systolic murmur. The female preponderance in this group was striking; 30 of the 34 patients were female. In the total patient group, 26.8 percent of the female and 5.5 percent of the male subjects manifested a mid-late or late systolic murmur at some time during the course of follow-up.

Follow-Up Results

Figure 1 depicts the age distribution of the 34 patients with a mid-late or late systolic murmur. Three patients were aged 6 to 10 years, 11 aged 11 to 15 years, and 8 aged 16 to 20 years, 8 aged 21 to 25 years and 4 aged 26 to 30 years. In four patients, three in the 11 to 15 year age group and one in the 16 to 20 year age group, the murmur has completely disap-

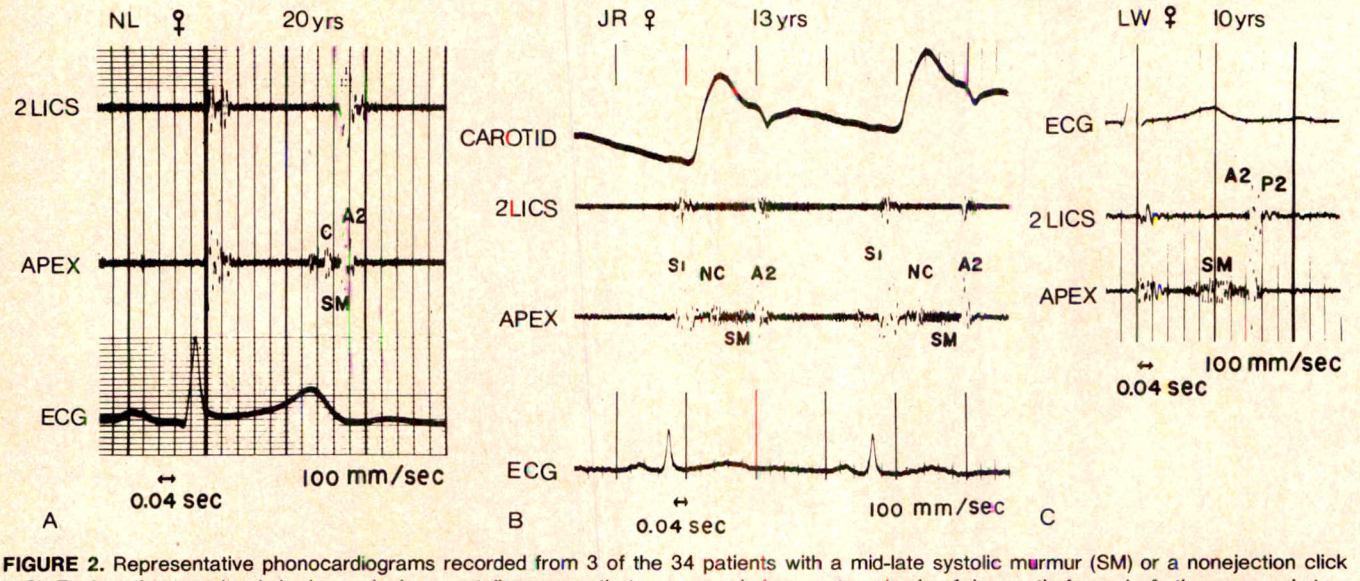

FIGURE 2. Representative phonocardiograms recorded from 3 of the 34 patients with a mid-late systolic murmur (SM) or a nonejection click (NC). Each patient previously had an apical pansystolic murmur that accompanied an acute episode of rheumatic fever. In **A,** there are only two distinct clicks audible at the apex. A definite systolic murmur was not audible and could not be demonstrated. In **B,** a nonejection click was recorded toward the end of the first third of systole. The click is followed by a plateau murmur that extends to the aortic component of the second heart sound. **C** demonstrates the typical mid-late systolic murmur noted in the majority of the 34 patients. The murmur begins in mid-systole and extends to the second heart sound. A_2 = aortic component of second heart sound; C = click; CAROTID = indirect carotid pulse tracing; P_2 = pulmonary component of second heart sound; S_1 = first heart sound at apex; 2LICS = second left intercostal space.

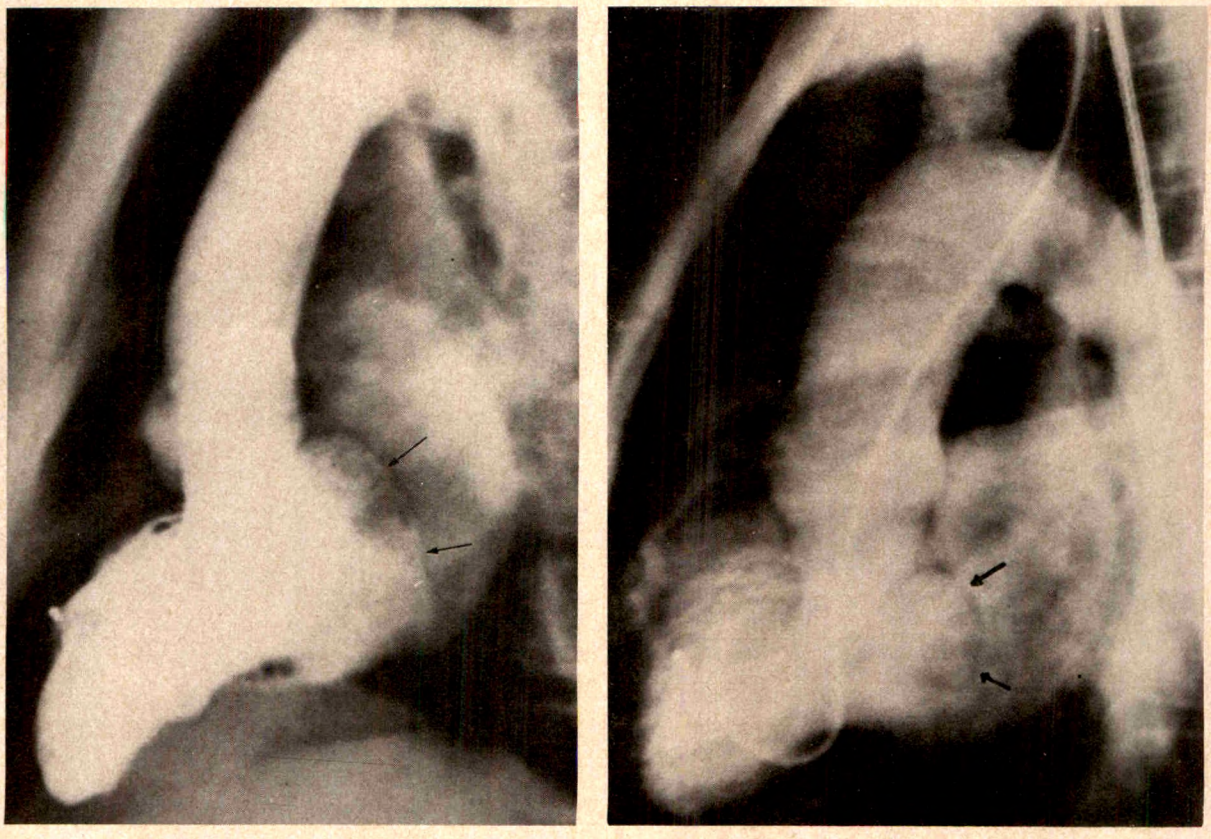

FIGURE 3. Selective left ventricular angiocardiograms (systolic phase, lateral view) obtained from two patients with known rheumatic heart disease and mid-late systolic murmurs. The films were taken during periods of regular sinus rhythm. Prolapse of the mitral valve is marked by the **arrows.** There is associated mitral regurgitation in both instances.

peared. Even in a meticulous screening program these patients would not ordinarily be considered to have heart disease.

The mid-late or late systolic murmurs were recognized as early as 1 month and as late as 9 years after the first and only acute episode of rheumatic mitral valvulitis (Table II). In approximately one third of the patients the systolic murmur developed within 1 year. In slightly more than half of the patients, the murmur appeared within 1 to 5 years, and in slightly less than one third of the patients more than 5 years elapsed before the murmur was recognized.

A distinct nonejection click was appreciated in 4 of the 34 patients. In the majority, the timing of the murmur could best be described as mid-late systolic. This is best illustrated in the phonocardiogram, which shows no murmur in the first third or perhaps the first half of the systolic period. Then after the quiescent period there is a plateau or crescendo murmur that extends to the aortic component of the second heart sound (Fig. 2). In the minority are those patients with only a very short late systolic murmur. The mid-late systolic murmurs encountered in this group of 34 patients, as observed previously[14] in related cases, appear to vary in response to changes in hemodynamic state. In any one patient a change in intensity, duration, timing and configuration of the mid-late systolic murmur could be anticipated after a

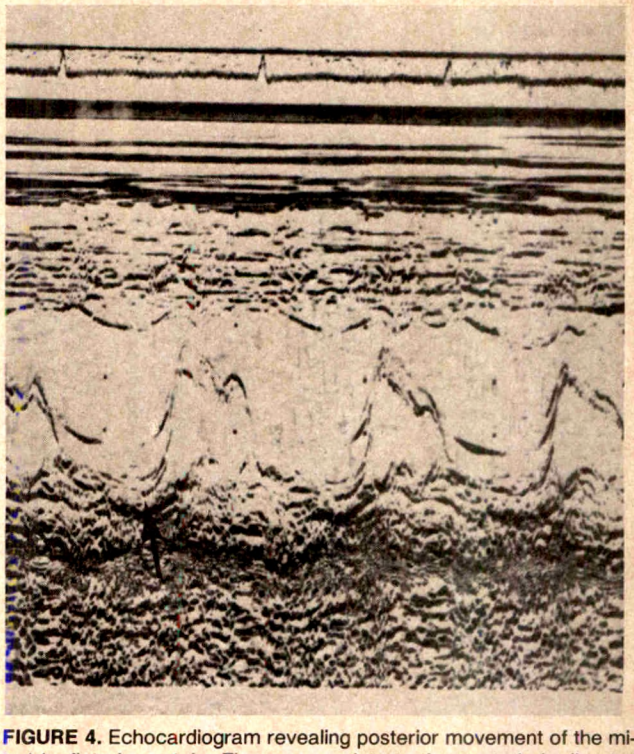

FIGURE 4. Echocardiogram revealing posterior movement of the mitral leaflets in systole. The **arrow** points to the posteriorly directed concavity that appears in late systole, which is diagnostic of systolic prolapse of the mitral valve.[15]

change in the patient's emotional state, activity pattern or position.

Angiocardiographic findings: Three of the 34 patients with a mid-late systolic murmur underwent cardiac catheterization and angiocardiographic studies in the early 1960's because they were thought to have a cardiac abnormality independent of the rheumatic heart disease. A recent review of the three biplane selective left ventricular angiocardiograms revealed that two of the three patients had evidence of systolic ballooning of the mitral valve into the left atrium (Fig. 3).

The patient whose angiocardiogram is shown at left in Figure 3, was studied in 1962 at age 12 years when an apical blowing mid-late systolic murmur was clearly audible. Six years previously the patient experienced his first and only attack of acute rheumatic fever. For the past 4 years there has been no evidence of a heart murmur and one could not be elicited during a recent examination by exercise, Valsalva maneuver or pharmacologic stimulation. In addition, a recently recorded echocardiogram of good technical quality was interpreted[15] as normal. On the basis of all current evidence we have concluded that this patient's mitral valve is now normal.

The angiocardiogram shown at right in Figure 3 illustrates a second example of a patient with a mid-late systolic murmur and a prolapsed mitral valve due to underlying rheumatic mitral valve disease. Cardiac catheterization and angiocardiography were performed in this patient in 1962 at age 6 years. A small patent ductus arteriosus was demonstrated in addition to the prolapsed mitral valve. The mid-late systolic murmur so clearly audible in 1962 has become shorter and softer over the years. Currently, in the resting state, the mid-late systolic murmur, so clearly audible earlier, is no longer audible. A faint late systolic blowing murmur can occasionally be heard after exercise, indicating that healing is not yet complete. A recently recorded echocardiogram (Fig. 4) demonstrated mitral valve prolapse.

Discussion

Mid-late or late systolic murmurs and nonejection clicks of rheumatic origin are probably more numerous than previously suspected. The 34 patients with rheumatic heart disease and a late systolic murmur or a nonejection click reported here all had minimal mitral regurgitation, as evidenced by absence of symptoms, repeatedly normal electrocardiograms and a normal cardiac silhouette on serial chest X-ray examinations. Within the age span encompassed by these patients, the more severe grades of mitral regurgitation do not appear to produce nonejection clicks or late systolic murmurs. The evolution of a mid-late or late systolic murmur from the pansystolic murmur accompanying acute or subacute rheumatic mitral valvulitis can probably be regarded as a sign of healing. Especially in female patients, the early components of the pansystolic murmur tend to disappear first with healing. Female patients are five times more likely than male patients to have a late systolic murmur.

Serial electrocardiograms from the patients with late systolic murmurs were reviewed in detail, with particular reference to T wave abnormalities. Review of several hundred electrocardiograms focusing especially on leads II, III, and aVF uncovered no instance of T wave abnormalities. The two patients with angiographically demonstrated prolapse of the mitral valve had consistently normal T waves.

The mitral click and late systolic murmur of nonrheumatic origin, on the other hand, are frequently associated with T wave abnormalities, even in the first 2 decades of life. The familial variety of mitral click and late systolic murmur is characteristically associated with T wave inversions,[8] commonly seen in lead aVF, but the left precordial leads may also show these changes. In cases of late systolic murmur or click of familial origin, there is an unusual mobility of the T waves, which may appear normal on one examination and abnormal on another. Serial electrocardiograms are therefore necessary to demonstrate the expected T wave inversion.

Clinical implications: We draw the following conclusions from the data and discussion in this report:

1. In young patients with disease of obscure or indefinite origin, the finding of a late systolic murmur or nonejection click in association with a normal electrocardiogram should serve as supportive, but not conclusive, evidence favoring a diagnosis of underlying rheumatic heart disease. Thus, other considerations being equal, antistreptococcal prophylaxis would seem appropriate.
2. Since none of the patients with known rheumatic heart disease and only a late systolic murmur or nonejection click had T wave abnormalities, one can assume with some degree of assurance in the young patient that late systolic murmurs or clicks associated with T wave abnormalities are due to nonrheumatic factors. In these patients antistreptococcal prophylaxis is therefore probably unnecessary.
3. Billowing of the mitral valve into the left atrium may occur as a consequence of what appears clinically to be relatively mild rheumatic mitral valve disease. The evidence now suggests that in some cases this lesion may heal spontaneously resulting in a normally functioning valve; in others, even in the absence of a systolic murmur or click, mitral valve prolapse may persist.

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Tetralogy of Fallot: A Morphometric and Geometric Study

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Fourteen examples of tetralogy of Fallot were studied by morphometric and geometric methods, and the findings compared with results from 10 normal hearts. The data show that in Fallot's tetralogy the conal septum is deviated anteriorly. The infundibulum, although narrow, is similar to, or of greater length than, that of the normal heart. This finding is not in agreement with recent observations suggesting that the anomaly represents lack of growth of the pulmonary conus.

Our results further demonstrate that the aorta is dextroposed in Fallot's tetralogy and that in the majority of cases absorption of the right extremity of the conoventricular flange has led to aortic-tricuspid fibrous continuity. The overall findings indicate that conal rotation has occurred in addition to anterior deviation. The data are interpreted as supporting a hypothesis of "lack of conal inversion" and conal malseptation as the morphogenetic mechanisms in tetralogy of Fallot.

The embryogenesis of the underlying malformations of tetralogy of Fallot is still much debated. The "classic" concept of this anomaly was propounded by Von Rokitansky[1] in 1875. He suggested that malseptation of the truncus at the expense of the pulmonary artery produced the tetralogy since the anteriorly deviated conal septum would no longer be able to contribute to the formation of the ventricular septum.

This concept was subsequently supported by Abbott,[2] De La Cruz and his co-workers[3,4] and Van Mierop and Wiglesworth.[5] It was challenged by Van Praagh et al.[6] in 1970, who considered that the pulmonary infundibulum in Fallot's tetralogy was "too short, too narrow and too shallow." They stated that this feature and others in tetralogy could best be explained on the basis of underdevelopment of the subpulmonary infundibulum. However, in a morphometric and geometric study demonstrating that the pulmonary infundibulum was of normal length in Fallot's tetralogy, Goor et al.[7] suggested that the condition was typified by dextroposition of the aorta, counterclockwise rotation of the conus and anterior deviation of the conal septum.

In view of this uncertainty regarding morphogenesis, we investigated cases of tetralogy of Fallot using geometric and morphometric techniques and compared our results with similar measurements of normal hearts. In addition, we paid particular attention to the structures surrounding the ventricular septal defect, since some recent investigators[8,9] have described an "intracristal" defect in some cases of tetralogy.

Material and Methods

Definition of Terms

A clear definition of terms is necessary since confusion exists regarding the terminology of conal structures. This is particularly evident with relation to the term "crista supraventricularis." We therefore present a definition of

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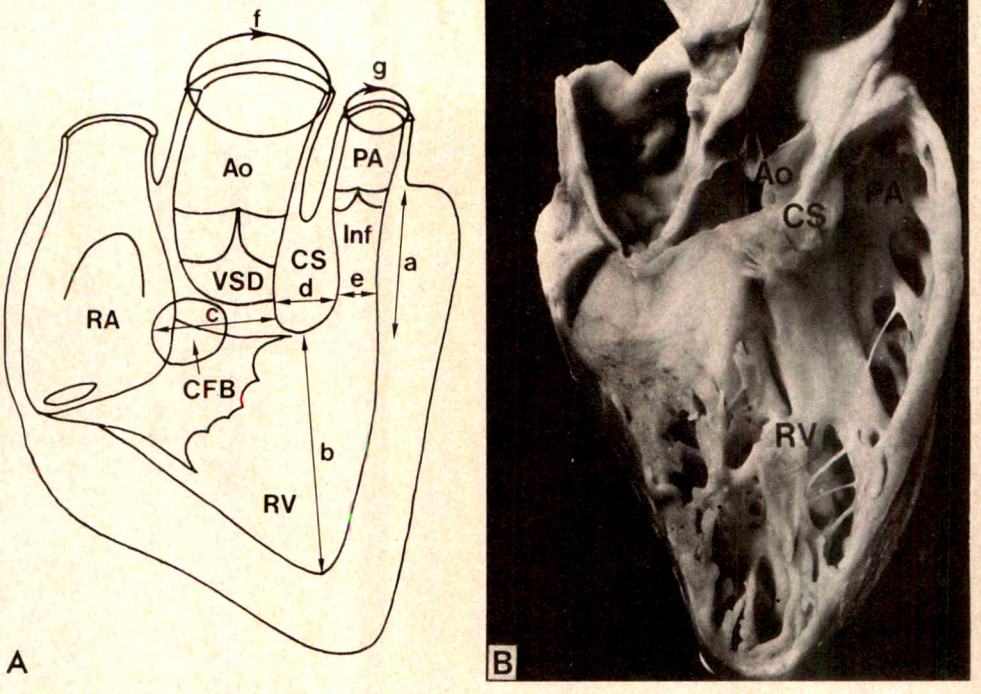


FIGURE 1. Morphometric measurements. **A,** diagram showing the measurements made in specimens of tetralogy of Fallot. The letters a to g indicate the dimensions recorded as described in the text. **B,** photograph of a specimen of a normal heart after bisection in the sagittal plane. Note how the specimen approximates the situation in Fallot's tetralogy and how directly comparable measurements can be taken. Ao = aorta; CFB = central fibrous body; CS = conal septum; Inf = infundibulum; PA = pulmonary artery; RA = right atrium; RV = right ventricle; VSD = ventricular septal defect.

terms in which we believe the controversial aspects are minimized.

Conal septum: This structure is the embryonic septum between the aortic and pulmonary conuses. As thus defined, it may occupy different positions in normal and abnormal specimens. In the normal heart it can be considered to possess two segments. The first segment lies between the aortic and pulmonary valves and forms part of the interventricular septum, blocking the sinistro-anterior portion of the primary bulboventricular foramen. The second segment stretches from this septal component to the parietal wall of the right ventricle and forms an integral part of the crista supraventricularis.

In hearts with tetralogy of Fallot, the entire proximal edge of the septum is considered to span the cavity of the right ventricle as a supraventricular structure. In these hearts, therefore, the septum possesses a free edge and septal and parietal insertions.

Conoventricular flange: This structure is considered to represent the inner curvature of the heart tube after bulboventricular looping.[10,11] It is the small segment of ventricular musculature that, after the looping process, intervenes between the atrial and bulbar (or conal) segments of the heart tube. In a recent embryologic study[11] it was termed the bulboatrioventricular ledge to indicate that it was originally composed of components from all three cardiac segments. During the normal development of the heart, the middle portion of the flange is absorbed to allow the aortic outflow tract to contact the left ventricle. This process, first described by Pernkopf and Wirtinger[12] and subse-

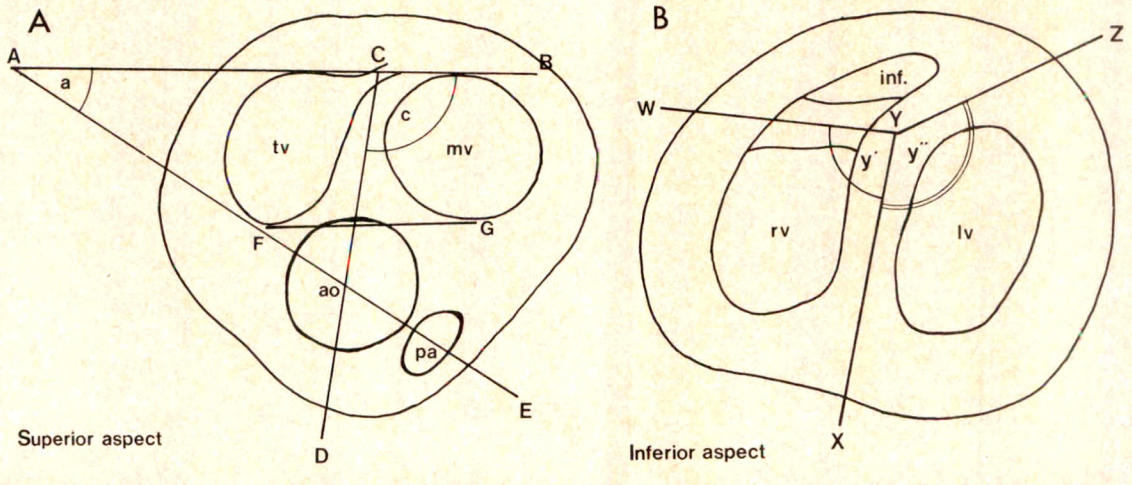


FIGURE 2. Geometric measurements. **A,** diagram of the superior aspect of the heart after removal of the atrial chambers and the great arteries. The lines constructed and angles measured are indicated. **B,** similar diagram of measurements and angles taken on inferior surface of the heart. ao = aorta; inf = infundibulum; lv = left ventricle; mv = mitral valve; pa = pulmonary artery; rv = right ventricle; tv = tricuspid valve. See text for letter abbreviations.

TABLE I

Measurements in 10 Normal Hearts and 14 Hearts with Tetralogy of Fallot

Case no.	Age (yr)	Length Infund. (a) (mm)	Length RV (b) (mm)	Aortic Conus (c) (mm)	Conal Septum (d) (mm)	Pulmonary Conus (e) (mm)	Aortic Circumf. (f) (mm)	Pulm. Circumf. (g) (mm)	Angle of GA (a) (°)	Angle of IAS (c) (°)
				A. Normal Hearts						
1	10/12	12	30	6	2	6	27	28	44	94
2	1 9/12	13	38	10	1.5	8	33	35	57	95
3	5	21	52	13	2.5	12	42	42	48	87
4	1	11	21	7	2	6.5	25	25	58	96
5	36	25	70	17	5	18	58	60	60	95
6	5	20	53	12	3	12	42	48	53	101
7	1 10/12	14	35	11	2.5	10	34	34	57	99
8	8/12	12	29	8	3	7.5	30	22	46	93
9	8/12	15	33	9	2	8	28	28	45	97
10	14	16	55	17	2.5	16	58	56	67	96
				B. Hearts with Tetralogy of Fallot						
1	7 hr	9	12	5	3	2	18	9	17	97
2	8	22	36	17	8	3	44	31	40	94
3	7/12	15	21	12	4	4	32	13	32	93
4	7 6/12	20	36	20	8	5	51	33	38	94
5	3/12	12	19	10	4	3	25	11	37	98
6	6	21	42	20	10	4	50	14	32	93
7	7/12	9	34	12	4	2	31	3	26	96
8	43	29	49	22	10	10	75	39	28	93
9	4/12	14	20	9	6	3	25	13	29	98
10	3/52	10	20	7	5	2	23	15	32	95
11	3/12	10	28	9	4	3	19	10	31	94
12	2/12	15	20	10	5	4	21	12	38	100
13	18/12	23	23	11	7	6	32	19	31	96
14	37	23	61	15	8	9	67	33	37	93

Circumf. = circumference; GA = great arteries; IAS = interatrial septum; Infund. = infundibulum; Pulm. = pulmonary; RV = right ventricle.

quent German embryologists, has been recently endorsed by several investigators.[11,13,14]

After this normal absorption, the right extension of this flange persists and, together with the parietal part of the conal septum, forms the normal crista supraventricularis.[11] However, in malformed specimens the flange can produce aortic-atrioventricular valve discontinuity.[5]

Crista supraventricularis: This term will be used here only to describe a structure in the normal heart. It is considered to be the supraventricular muscle mass that separates the pulmonary and tricuspid valves.[15] It is formed from two components,[11,12] the right extension of the conoventricular flange as the outer component and the parietal part of the conal septum as the inner component. In some hearts, the latter component extends toward the apex of the ventricle, where it fuses with a well formed septal trabecula (see later). This septal trabecula is not considered part of the crista supraventricularis.

Trabecula septomarginalis: This term is used to describe the extensive septal trabecula that extends from a position just beneath the pulmonary valve toward the ventricular apex and continues as the moderator band onto the parietal wall of the ventricle.

This definition corresponds to that given by Tandler[16] for a common variation of his trabecula septomarginalis. It is also in keeping with Keith's description[17] of the left septal band and the description by Lev and Saphir[18] of the septal muscle bundle. Although the term trabecula septomarginalis is now commonly used to describe only the moderator band, it is evident from the descriptions cited that the latter structure is a continuation of the septal trabeculation. Van Mierop et al.[10] used the term trabecula septomarginalis to describe both the septal band and the moderator band, and we follow their precedent.

The trabecula septomarginalis is therefore considered to possess anterior and posterior limbs at its superior extent. The septal part of the conal septum is inserted between these limbs in the normal heart, and the papillary muscle of the conus arises from the posterior limb. The anterior papillary muscle arises from the trabecula septomarginalis toward the ventricular apex, and the moderator band frequently fuses with the parietal extension of the conal septum after it has crossed the ventricular cavity. An annulus is therefore formed between the conal septum, its parietal extension and the trabecula septomarginalis.

Case Material

Twenty-four hearts were studied, 14 specimens of tetralogy of Fallot and 10 normal hearts. To be considered an example of tetralogy, a heart was required to possess the combination of pulmonary infundibular narrowing, ventricular

septal defect, overriding aorta and right ventricular hypertrophy in the presence of mitral-aortic fibrous continuity. Patients with Fallot's tetralogy ranged in age from 7 hours to 43 years. The normal subjects were 8 months to 36 years old (Table I).

Morphometric Measurements

The following morphometric observations were recorded in all specimens (Fig. 1):

I. The infundibular length (a) was measured from the septal commissure of the pulmonary valve to the most inferior point of the conal septum.

II. The length of the right ventricle (b) was recorded from the ventricular apex to the most inferior part of the conal septum.

III. The proportions of the embryonic bulbus occupied by aortic (c) and pulmonary (e) outflow tracts and the thickness of the conal septum (d) were noted.

In the specimens of Fallot's tetralogy these measurements were taken on a line that passed from the most posterior part of the aortic outflow tract, beneath the conal septum to the anterior wall of the right ventricle (Fig. 1A). To produce a comparable situation in the normal hearts it was necessary to make a sagittal section through the heart that bisected the aortic outflow tract. This section then delineated the dimensions of both outflow tracts together with the thickness of the conal septum (Fig. 1B).

IV. The circumferences of the aortic (f) and pulmonary (g) external orifices were measured.

Geometric Measurements

These measurements were recorded after removal of the atrial chambers and great arteries had revealed the fibrous valvular rings and a transverse cut through the ventricles had been made in the plane of the atrioventricular rings. These procedures made it possible to place a glass sheet upon the superior and inferior surfaces of the remaining cardiac segment and to record the salient features on superimposed transparent paper.

On the superior aspect the following lines were constructed (Fig. 2A):

I. Through the posterior margins of the A-V rings (ACB).

II. Through the anterior margins of the same rings (FG).

III. Through the mid-points of the semilunar valve rings (AFE).

IV. Along the plane of the interatrial septum (CD).

The angles of the great arteries (a) and the interatrial septum (c) were then calculated relative to the line ACB. In the normal hearts these measurements were recorded before the outflow tracts were sectioned.

On the inferior surface of the specimens of Fallot's tetralogy the following lines were constructed (Fig. 2B):

I. Along the posterior interventricular septum (XY).

II. Along the anterior interventricular septum (YZ).

III. Along the conal septum (WY).

The angles subtended by the conal septum (y′) and the anterior septum (y″) were then recorded relative to the posterior septum.

The recorded measurements from these various procedures are indicated in Table I. For comparative purposes the observations were presented as follows:

A. The length of the infundibulum (a) was recorded as a fraction of the entire right ventricular length (a + b) recorded as unity.

B. The proportion of the total width of the embryonic bulbus (c + d + e), expressed as unity, as occupied by the aortic outflow tract (c), conal septum (d) and pulmonary tract (e).

C. The ratio of the circumference of the pulmonary artery compared with that of the aorta expressed as unity.

D. The angle of the great vessels in two groups. In the same diagram it was also possible to illustrate the position of the aorta by constructing circles to indicate the relation of the aortic valve ring to the lines FG and CD.

The data used for each of these comparisons were subsequently submitted to statistical analysis using Student's *t* test and a confidence level of 0.5 percent (Table II).

TABLE II

Data Submitted to Statistical Analysis Using Student's *t* test*

Measurements (see Fig. 1)	Fallot (14 specimens)	Normal (10 specimens)	*P*
Length of pulmonary conus expressed as part of length RV [(a/(a + b)]	0.36 ± 0.08	0.28 ± 0.03	>0.005
Proportion of embryonic conus occupied by pulmonary conus [e/(c + d + e)]	0.18 ± 0.05	0.43 ± 0.02	>0.005
Circumference of pulmonary artery compared with that of aorta (g/f)	0.50 ± 0.16	1.02 ± 0.05	>0.005
Angle of great arteries a°	32 ± 6.04	53.5 ± 7.59	>0.005

* Values expressed as mean ± standard deviation.
P = level of significance (hearts with tetralogy vs. normal specimens); RV = right ventricle.

Results

Basic Anatomy of the Right Ventricle

In the normal heart, the right ventricle possesses inflow and outflow portions, the boundary between the two being the annulus formed by the conal septum, its parietal extension and the trabecula septomarginalis (Fig. 3).

In Fallot's tetralogy these morphologic features are not observed, since the septal insertion of the conal septum is anterior to the trabecula septomarginalis (Fig. 4). Since the parietal insertion is also deviated anteriorly, the conal septum and conoventricular flange form distinct structures (Fig. 3). The infundibulum is a narrow channel situated anteriorly in the right ventricle. An intermediate ventricular segment communicates with the left ventricular outflow tract. The septal defect between this segment and the aortic outflow tract is bounded by the following structures: (1) anteriorly by the septal inser-

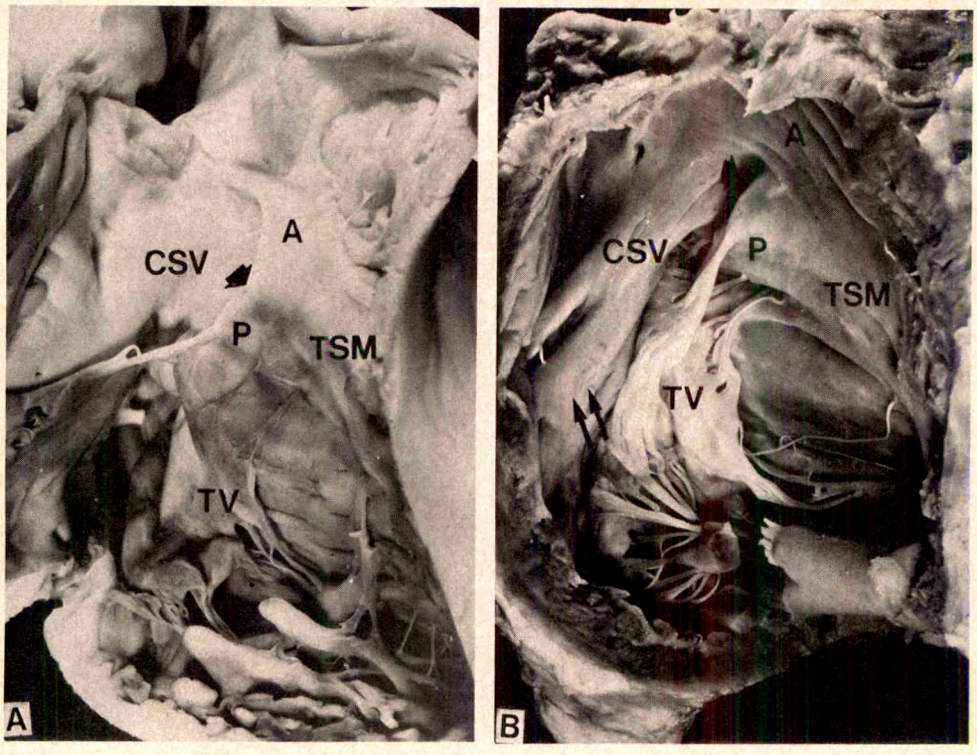


FIGURE 3. Photographs of specimens of normal hearts. **A,** taken as if looking from the right ventricular apex directly into the pulmonary outflow tract. The normal crista supraventricularis (CSV) separates the tricuspid (TV) and pulmonary valves. Its septal insertion **(thick arrow)** is between the anterior (A) and posterior (P) limbs of the trabecula septomarginalis (TSM). **B,** taken from the ventricular apex looking towards the tricuspid valve (TV). Note that a prominent trabecula extends from the parietal insertion of the crista supraventricularis **(double arrows)** toward the ventricular apex, where it joins with the trabecula septomarginalis. The right ventricle is therefore divided into an inflow and an outflow portion. Again note the septal insertion **(thick arrow)** of the crista supraventricularis between the limbs of the trabecula septomarginalis.

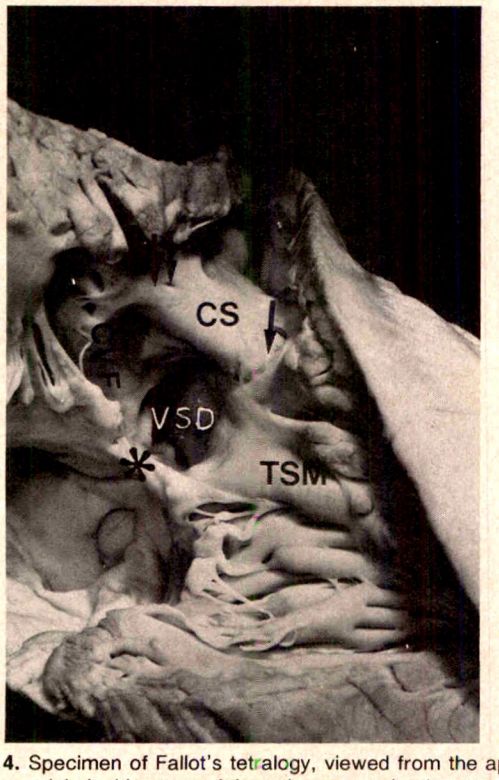


FIGURE 4. Specimen of Fallot's tetralogy, viewed from the apex of the right ventricle looking toward the pulmonary valve (compare with Fig. 3A). The conal septum (CS) is divorced from the right margin of the conoventricular flange (CVF). The septal **(single arrow)** and parietal **(double arrows)** insertions of the conal septum are both deviated anteriorly, thus constricting the pulmonary outflow tract. The septal insertion is anterior to the trabecula septomarginalis (TSM), which together with the muscular ventricular septum forms the floor of the defect (VSD). At the posterior edge of the defect an area of tricuspid-aortic continuity is visible (*). The roof of the defect is formed by the subaortic conus, between the conoventricular flange and the conal septum.

tion of the conal septum, which fuses with the anterior segment of the ventricular septum in front of the trabecula septomarginalis; (2) inferiorly by the crest of the muscular septum, which is reinforced by the trabecula septomarginalis; (3) posteriorly by the ventricular septal structures fusing with the atrioventricular annulus; and (4) above the atrioventricular annulus by the right margin of the conoventricular flange, which forms the aortic conus in this position.

The degree of development of the conoventricular flange varied in different specimens. In the majority, there was direct fibrous continuity between the aortic and tricuspid valves (Fig. 4). In some specimens the flange completely separated these two valves, but the tricuspid valve was continuous with the mitral valve and thence with the aortic valve by way of the central fibrous body (Fig. 5A). In two specimens, however, a bar of muscle completely separated the aortic and tricuspid valves, stretching to the crest of the ventricular septum and producing a complete muscular rim to the ventricular septal defect (Fig. 5B). Although the ridge appeared as a thick band from its inferior aspect, dissection from above suggested that it represented a reduplication of the heart wall (Fig. 6A); bisection of the ridge resulted in confirmation of this opinion (Fig. 6B).

Morphometric Observations

In the normal hearts the fraction of the right ventricular length (a + b) occupied by the pulmonary conus (a) averaged 0.28. In the specimens of tetralogy of Fallot (Fig. 7) this fraction was generally larger, falling below the normal mean value in only three specimens. The average value for the malformed specimens was 0.36 and the extreme was 0.50. The

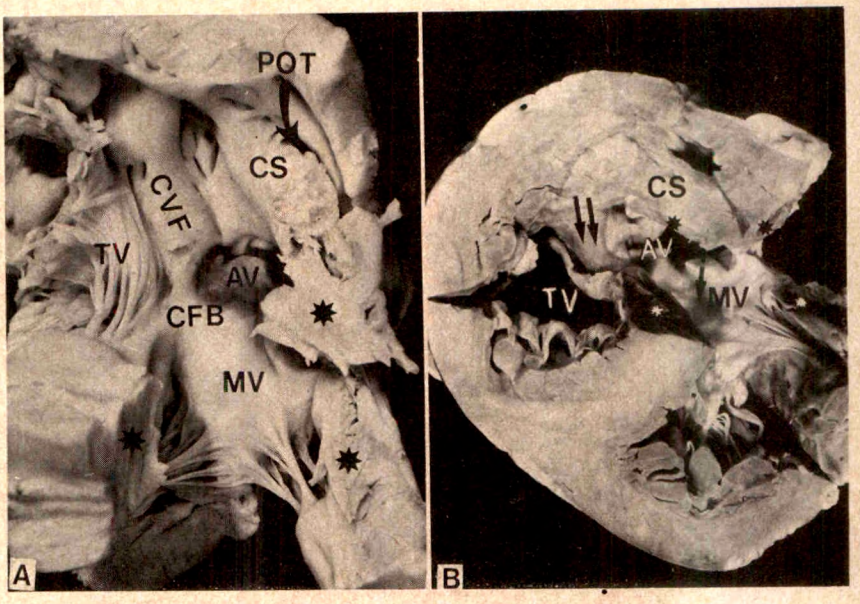


FIGURE 5. Specimens of Fallot's tetralogy showing various degrees of separation between aortic (AV) and tricuspid (TV) valves. **A,** specimen viewed from below after division of the ventricular septum (**) in which the right margin of the conoventricular flange (CVF) separates the greatest part of the valve rings. However, fibrous continuity is present between the tricuspid and mitral (MV) valves by way of the central fibrous body (CFB), and forms the posterior margin of the ventricular septal defect. Through the central fibrous body, continuity is also established between the aortic and tricuspid valves. **B,** specimen in which the ventricular septum has again been divided (**) to demonstrate the inferior aspect of the aortic valve. Although aortic-mitral valvular continuity is present **(single arrow)** a complete bar of muscle separates the aortic and tricuspid valves, and fuses with the tip of the ventricular septum **(double arrows).** The muscle bar forms the roof and posterior wall of the defect, and is the right margin of the conoventricular flange. The defect has been sectioned through its floor. CS = conal septum; POT = pulmonary outflow tract.

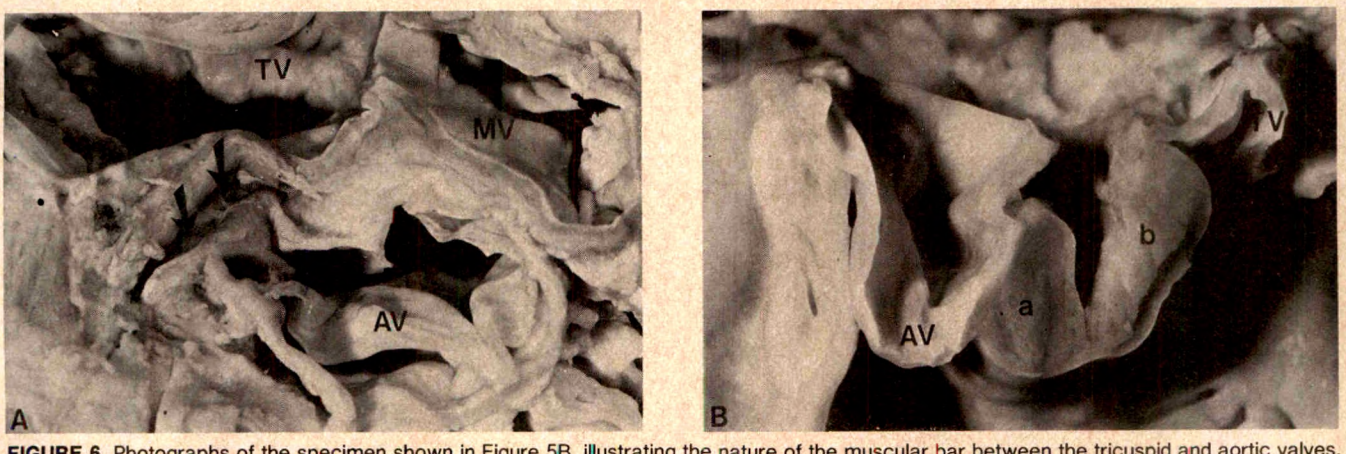


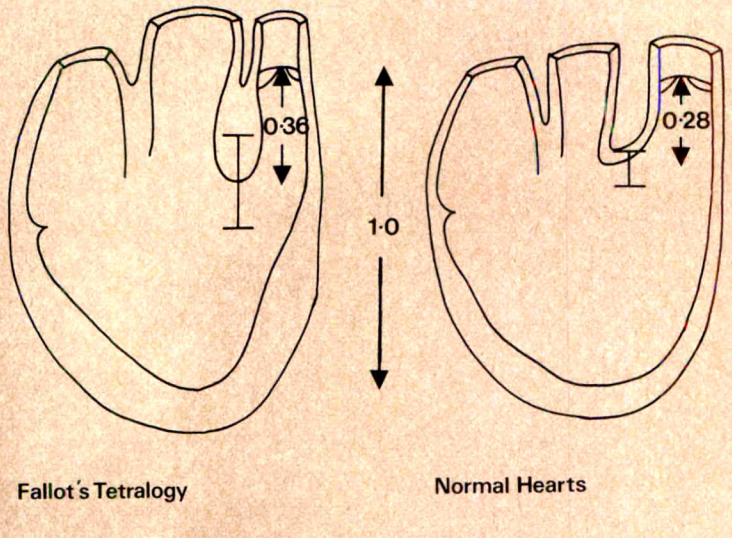
FIGURE 6. Photographs of the specimen shown in Figure 5B, illustrating the nature of the muscular bar between the tricuspid and aortic valves. **A,** superior view, the bar is dissected to demonstrate that although it appears as a solid ridge from below (Fig. 5B), it represents a reduplication of the heart wall **(double arrows). B,** the ledge after its bisection, viewed from the septal aspect. The reduplication is demonstrated, and the bulbar (a) and ventricular (b) components are clearly visible. AV = aortic valve; MV = mitral valve; TV = tricuspid valve.

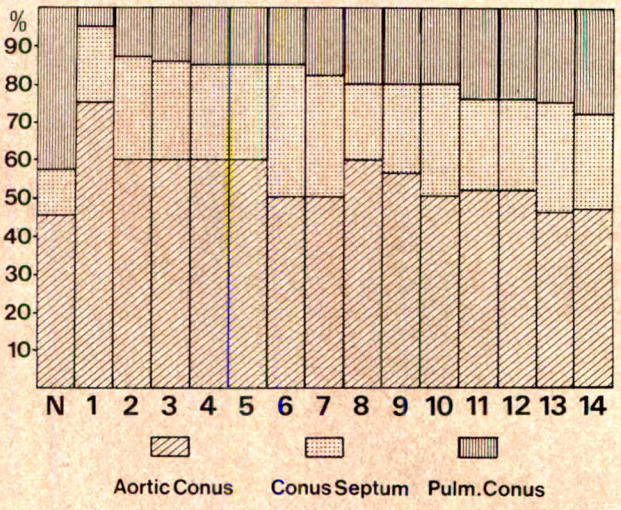
differences between the values in the two groups was statistically significant ($P > 0.005$). In the normal heart the embryonic bulbus was divided approximately evenly between the aortic (c) and pulmonary (e) outflow tracts, the respective average values being 45 and 43 percent, whereas the conal septum (d) occupied 12 percent of the width of the bulbus.

In Fallot's tetralogy the conal septum was grossly enlarged (average 25 percent) at the expense of the pulmonary conus (average 20 percent), whereas the aortic conus was also expanded (average 55 percent), again at the expense of the pulmonary conus (Fig. 8). The differences between the normal hearts and specimens of Fallot's tetralogy were statistically significant ($P > 0.005$). In normal specimens the pulmonary circumference was similar to the aortic circumference (1.02 to 1.00). In the specimens of Fallot's tetralogy, as might be expected,[19] it was markedly diminished, the average value being 0.50 with extremes of 0.70 and 0.16 (Fig. 9). The differences were again of considerable statistical significance ($P > 0.005$).

Geometric Measurements

These measurements showed that although the angle of the interatrial septum (c) was virtually identical in malformed and normal specimens (95° vs. 94°), the angle of the great arteries (a) was markedly different. In normal specimens this angle was 53.5° (range 44° to 67°); in specimens of tetralogy it was 32° (range 17° to 40°). These studies additionally showed that the aortic valve was dextroposed (in relation to the interatrial septum) and anteriorly deviated in the hearts with tetralogy compared with the normal hearts (Fig. 10). As with the other results, this finding was statistically significant ($P > 0.005$). In the normal hearts the angle of the conal septum (y′) was difficult to measure, but it subtended less than 90° to





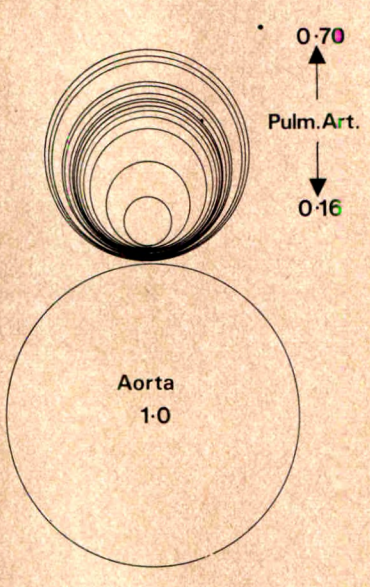


FIGURE 7 (upper left). Diagram illustrating the length of the infundibulum (measurement a) expressed as a ratio of the right ventricular length (measurement a + b). The illustrated infundibular length indicates the average value of this ratio in hearts with tetralogy of Fallot and normal specimens, and the scales indicate the range of measurements of the infundibular lengths.

FIGURE 8. (upper right) Diagram illustrating the mode of division of the embryonic bulbus in hearts with tetralogy of Fallot and normal specimens. The **hatched portions** represent measurements of the aortic conus (c), conal septum (d) and the pulmonary (Pulm.) conus (e) expressed as ratios of the measurement c + d + e. Column N represents the average values of 10 normal hearts, columns 1 to 14 represent individual measurements in the specimens with tetralogy of Fallot.

FIGURE 9 (lower left). Diagram showing the circumference of the pulmonary artery (Pulm. Art.) expressed as a ratio of the aortic circumference. Each circle represents the circumference of the pulmonary artery from individual specimens with Fallot's tetralogy, and the figures give the range of values. The ratio in the 10 normal hearts was 0.98 to 1.00.

the posterior septum. In the majority of specimens of Fallot's tetralogy this angle was equal to or greater than 90°.

Discussion

This study was based upon morphometric and geometric measurements obtained from formalin-fixed specimens. Undoubtedly artifacts have been introduced and some of the measurements may not be completely without bias. However, we believe that this quantitative approach gives a more reliable answer to the questions posed than could be provided by mere inspection of such hearts.

Conal Rotation and Malseptation

Our results are in agreement with findings in the similar morphometric and geometric study conducted by Goor et al.,[7] and we agree with these workers that Fallot's tetralogy is characterized by the morphogenetic features of conal rotation and conal malseption. The conal rotation is manifested by the demonstrated aortic dextroposition. Although Van Praagh et al.[6] considered this feature to be present only in cases with "severe pulmonary outflow tract obstruction," we agree with Goor et al.[7] that it is a hallmark of the anomaly. However, we also found that the aortic valve was anteriorly displaced in relation to the atrioventricular valve rings, and no longer occupied its normal "wedge" position (Fig. 10). Indeed, although we agree with Van Praagh et al.[6] that the normal aorta overrides the ventricular septum (Fig. 11A), we consider that the associated anterior deviation of the aortic valve in Fallot's tetralogy forms the major difference between the two conditions (Fig. 11B).

The conal malseption is shown by the anterior deviation of the conal septum. The rotation of the conus itself may have rotated the conal septum as judged by the divorce of its parietal insertion from the conoventricular flange. However, additional anterior deviation is indicated by the position of the septal insertion in front of the trabecula septomarginalis. This feature was described as a T insertion by

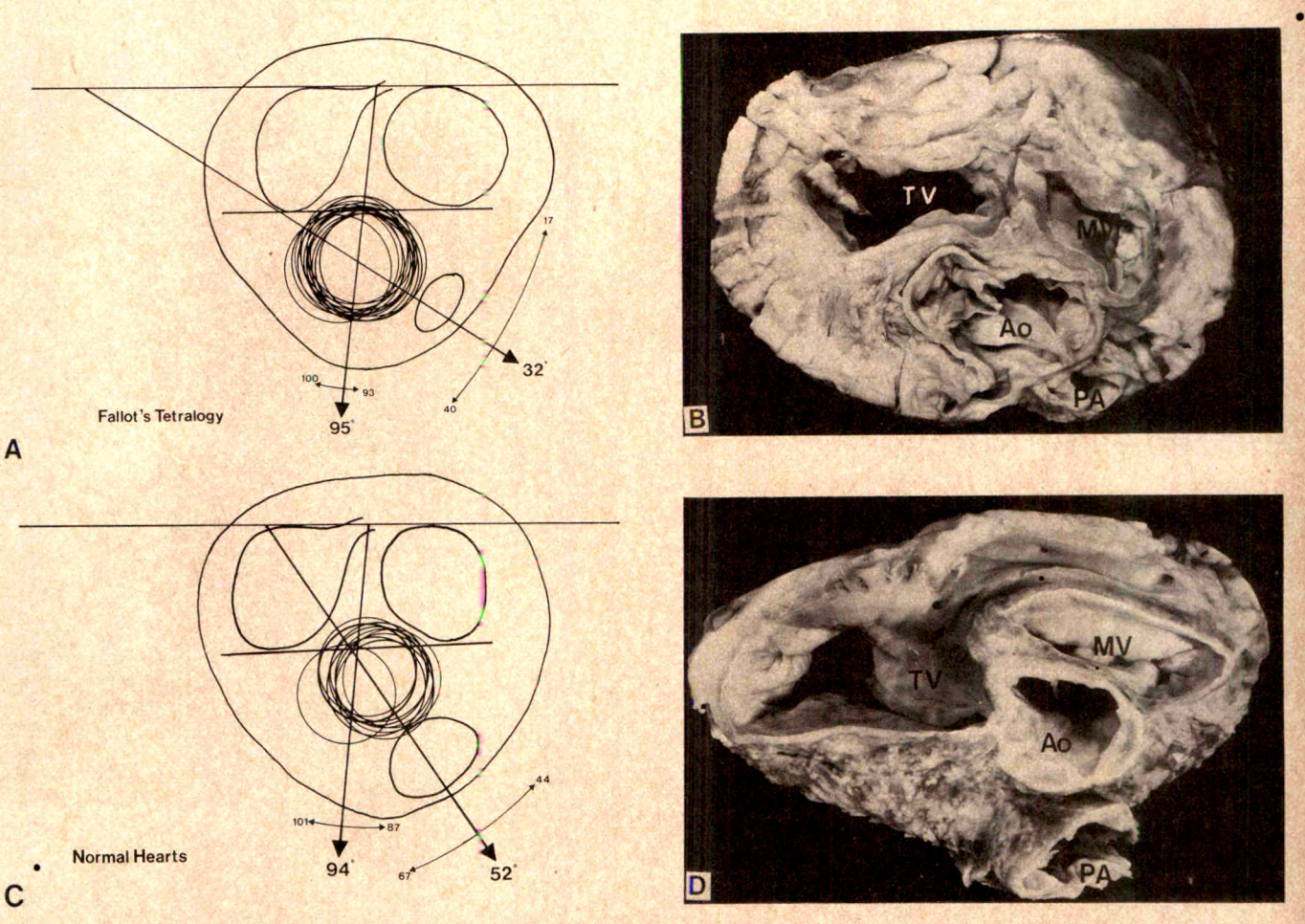


FIGURE 10. Diagrams illustrating the geometric values for hearts with Fallot's tetralogy **(A)** and normal hearts **(C)**. Photographs of typical specimens viewed from above are shown for comparison. **B** is a specimen with tetralogy of Fallot and **D** is a normal heart. Note that in Fallot's tetralogy, the angle of the great vessels is reduced and the aortic valve ring (Ao) is deviated anteriorly and to the right. Each circle in the position of the aorta in Panels **A** and **C** represents the position in an individual specimen. The figures indicate the average and extreme values for the angle of the great arteries (a) and the angle of the interatrial septum (c). PA = pulmonary artery; MV = mitral valve; TV = tricuspid valve.

Goor et al.[7] and was present in all our specimens. In this respect our findings are in agreement with theirs. Since they demonstrate that the conus is malseptated at the expense of the pulmonary artery, their data could be construed as supporting the classic hypothesis of truncal malseptation.[1]

Truncal malseptation cannot explain all features of the anomaly, since it alone could not produce the dextroposed and anteriorly deviated aorta. Additional conal malrotation is necessary to explain these features. Since both malrotation and malseptation are necessary, it also follows that we are unable to support the concept of the monology proposed by Van Praagh et al.[6] This concept itself was based upon conal maldevelopment, but its main point was lack of growth of the subpulmonary conus. However, our results, like those of Goor et al.,[7] indicate that the pulmonary infundibulum is of normal or increased length in Fallot's tetralogy. The question must now be posed whether Van Praagh himself considers the infundibulum underdeveloped, since in a personal communication to Goor and colleagues,[7] he stated that his measurements indicated the infundibulum to be of normal length.

Differential Conal Absorption Hypothesis

It is also significant that the embryologic observations[11,13,14] now favor the differential conal absorption hypothesis originally propounded by Pernkopf and Wirtinger[12] and other embryologists of the "German school." When Paul et al.[20] first considered the concept of conal absorption, they believed that it was insufficiently supported by embryologic evidence and promoted instead a conal growth hypothesis[21] that they considered to be supported by anatomic facts. Since then, the embryologic studies have vindicated the concept of conal absorption, and Van Praagh[22] now refers to "differential conal development."

We can speculate on the significance of differential conal development to the morphogenesis of tetralogy of Fallot. A vital feature of normal embryogenesis is the normal "inversion" of the conus that brings the aorta to a dextroposterior position.[14] At this stage a myoblastic ledge separates the developing semilunar and atrioventricular valves, and this ledge is the conoventricular portion of the inner curvature of the heart tube, or the conoventricular flange[11] (Fig. 12A). Subsequent absorption of this ledge accounts for a

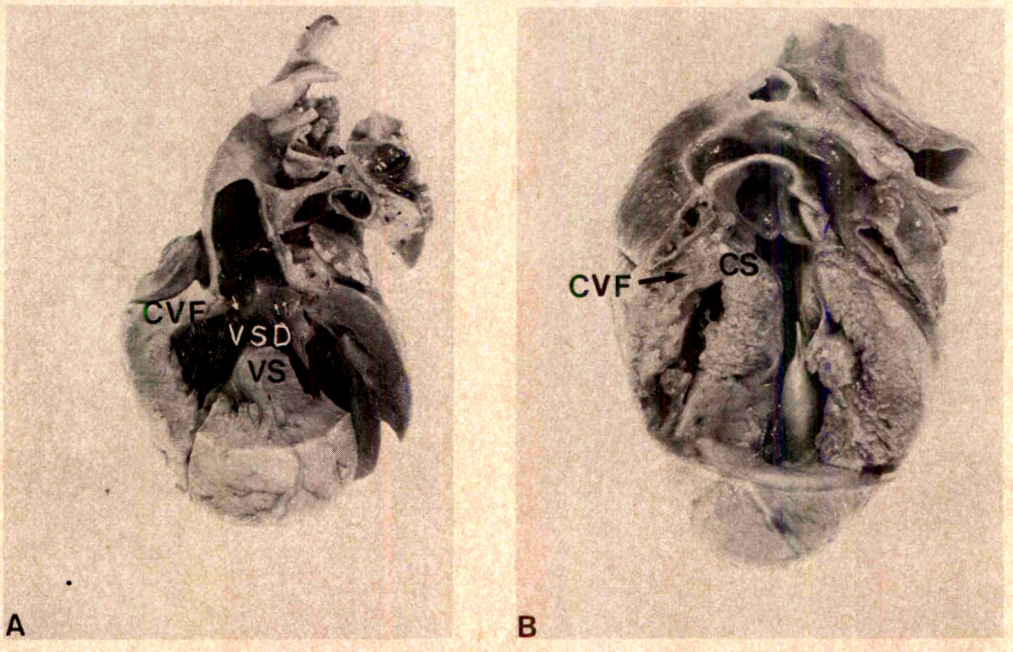


FIGURE 11. Photographs of a specimen with tetralogy of Fallot **(A)** and a normal heart **(B)** dissected to demonstrate the relation between the aortic valve ring and the ventricular septum. In each heart the frontal cut was made in similar positions, but in **A** did not remove the auricular tips. In the specimen with tetralogy of Fallot the conal septum is not visible, and a large defect (VSD) exists between the right margin of the aortic valve and the ventricular septum (VS). The aorta in this position arises from the right extremity of the conoventricular flange (CVF). The entire posterior rim of the aortic valve is visible, and areas of tricuspid-aortic **(single arrow)**, mitral-aortic **(double arrow)** and tricuspid-mitral continuity are seen. In the normal specimen (**B**), the conal septum (CS) is seen blocking the space between the ventricular septum and the conoventricular flange, and the aortic valve arises from the conal septum. The area of mitral-aortic continuity is not visible owing to the "wedge" position of the aortic valve ring. Note the normal overriding position of the aortic valve.

further shift of the aorta to the left ventricle and for the fibrous continuity normally present between the aortic and mitral valves (Fig. 12B). Should the normal inversion of the conus be incomplete, then the aorta would be in dextroposition (Fig. 12C). Absorption from this position would be insufficient to carry the aorta into its normal position above the left ventricle but could produce mitral-aortic continuity. Additional absorption would also be possible permitting fibrous continuity with the tricuspid valve (Fig. 12D). From this it follows that various degrees of absorption in the latter position would account for the observed discrepancies in aortic-tricuspid continuity (Fig. 3, A to C) in Fallot's tetralogy. It also follows that, when complete separation of the valves is present, it is the persisting right portion of the conoventricular flange that separates them (Fig. 6 A and B).

Crista Supraventricularis vs. Parietal Band

Rosenquist et al.[9] described identical findings, but interpreted this muscle bar as the inferior and proximal part of the infundibular septum. They therefore termed this structure the "parietal band" and considered that it fused with the deviated distal infundibular septum, which they termed the "crista supraventricularis," in the floor of the defect. Consequently, they described the defect as *intracristal.*

We believe that the differences in interpretation relate in part to the usage and abusage of the term "crista supraventricularis." Opinions differ about the structure composing the "crista supraventricularis," even in the normal heart. Our observations substantiate that part of the concept of Van Praagh[23] in which the "septal band" is separated from the crista. The "septal band" is the proximal extension of the structure originally described by Tandler[16] as the trabecula septomarginalis. The viewpoint that it is not a cristal structure is endorsed by the embryologic observations of Goor et al.,[14] and Anderson et al.,[11] who substantiated the isolated opinion of Pernkopf and Wirtinger.[12] Furthermore, the studies of Anderson et al.[11] indicated that the normal crista supraventricularis, or the "parietal band" of Van Praagh,[23] had two components, namely, the parietal insertion of the conal septum and the right margin of the conoventricular flange.

This concept is in contrast with the opinion of Paul et al.[20] and the data of Goor et al.,[14] each of which correlated the "parietal band" solely with the conal septum. The opinion of Paul et al.[20] was illustrated by reference to truncus specimens in which the "parietal band," or crista, was believed to be absent. However, others[24] have indicated that a diminutive crista persists in truncus specimens, correlating well with the hypothesis that this structure represents the right extension of the conoventricular flange as now espoused. Furthermore, Van Mierop[25] recently suggested a further modification of this nomenclature based upon his embryologic observations. He would restrict the term "crista supraventricularis" to that part of the ventricular tissues derived from the fused conal ridges. He considers that the parietal and septal bands are separate from the crista, both anatomically and embryologically. When all three structures

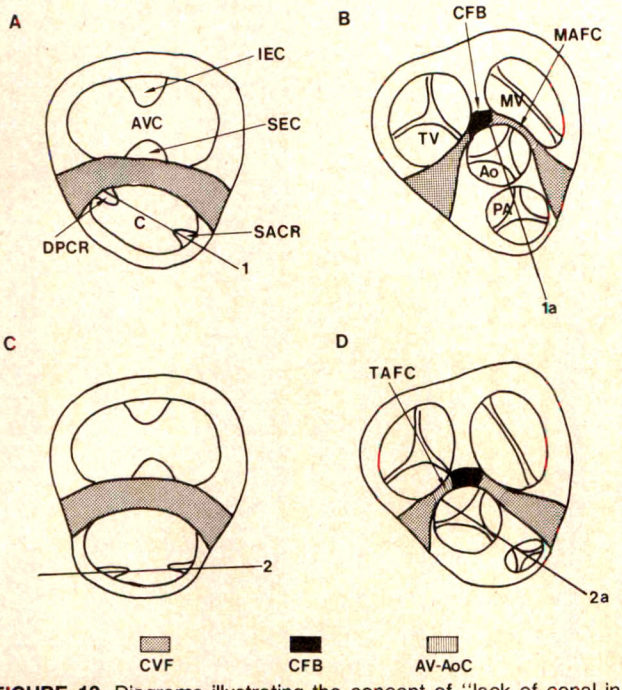


FIGURE 12. Diagrams illustrating the concept of "lack of conal inversion"[13] and conal absorption.[10] **A** represents the position in the normal heart after normal conal inversion. The conal ridges are in dextroposterior (DPCR) and sinistro-anterior (SACR) positions, and their orientation is indicated by line 1. **B,** absorption of the conoventricular flange (CVF) allows the aorta (Ao) to migrate above the left ventricle. This process also facilitates the occurrence of mitral-aortic fibrous continuity (MAFC) and establishment of the central fibrous body (CFB). The final angle of the arteries differs from the orientation of the conal ridges (compare lines 1 and 1a). **C** shows the situation of the conus after postulated "lack of conal inversion" (compare lines 1 and 2). It also shows anterior deviation, considered to be a morphogenetic feature in Fallot's tetralogy. Conal absorption from the position **(D)** would enhance fibrous continuity between both the tricuspid valve (TAFC) and the mitral valve (MV) with the aortic valve (AV-AoC). The angle of the great arteries would be less than the normal (compare lines 2a and 1a). AVC = atrioventricular canal; C = conus; IEC = inferior endocardial cushion; PA = pulmonary artery; SEC = superior endocardial cushion; TV = tricuspid valve.

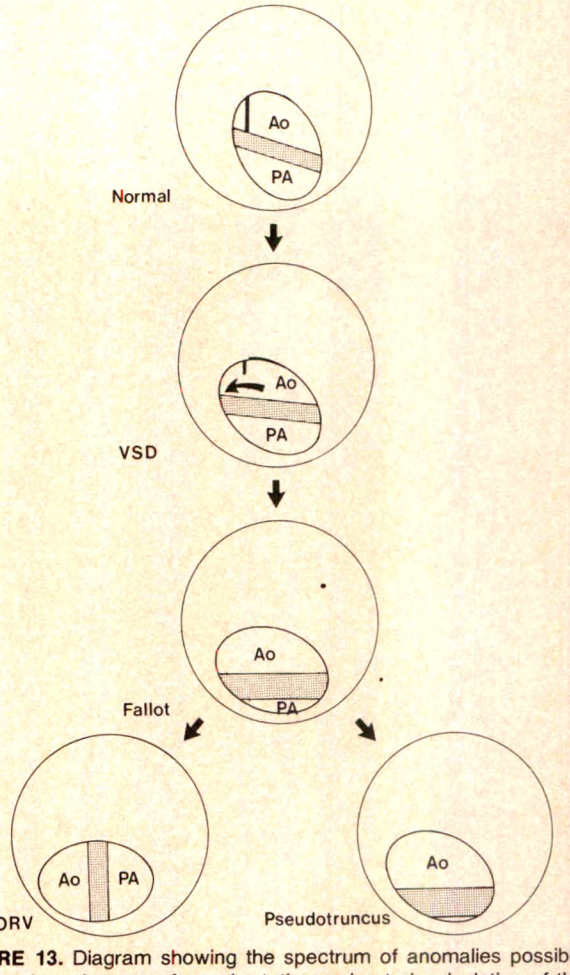


FIGURE 13. Diagram showing the spectrum of anomalies possible after various degrees of conal rotation and anterior deviation of the conal septum. In the normal position, the gap between ventricular and conal septa is filled by the membranous septum **(solid black line).** After minimal conal rotation, it can be postulated that the membranous septum would not fill this gap, and a ventricular septal defect (VSD) would result. Further rotation together with anterior deviation of the conal septum would result in Fallot's tetralogy. From this point, increased anterior deviation would produce pseudotruncus arteriosus, whereas continued rotation coupled with a normally positioned septum would result in double outlet right ventricle (DORV). Ao = aorta; PA = pulmonary artery.

are correctly aligned, as in the normal heart, such a definition cannot be faulted. However, Van Mierop[25] has indicated that the components may not be so aligned. If, when the components are not aligned, this definition is adhered to and the term "crista supraventricularis" is restricted to the conal septum, then the nomenclature would continue to be admirable. However, we have demonstrated that other investigators have used widely varying definitions of the terms parietal and septal bands, and have regarded them as integral parts of the "crista."

Thus, within the definition of Rosenquist et al.,[9] the defect in Fallot's tetralogy with aortic-tricuspid discontinuity is indeed intracristal. However, if any of the other definitions indicated is applied to this situation, then the defect cannot be considered intracristal. This is because the cases of Fallot's tetralogy with aortic-tricuspid discontinuity represent cases in which the building blocks of the normal right ventricle are not correctly aligned, but are recognizable as discrete structures. Thus, in our opinion, the muscle bar that separates the aortic and tricuspid valves is the conoventricular flange, or the parietal band of Van Mierop.[25] Rosenquist et al.,[9] in contrast, believe it to be the proximal conal septum. The muscular tissues separating the arterial outflow tracts are considered by us to represent the conal septum, and would be termed the crista supraventricularis by Van Mierop.[25]

Rosenquist et al.[9] would name this structure the distal conal septum. The muscular tissue forming the floor of the defect and reinforcing the muscular ventricular septal crest is the trabecula septomarginalis, or the septal band of Van Mierop,[25] whereas Rosenquist et al.[9] have described this structure as another part of the proximal conal septum. Van Mierop[25] has moved away from his earlier definition of the trabecula septomarginalis which we have adopted. Nonetheless, neither his nor our present definitions

would include this structure as part of the "crista," and neither would the definition of Van Praagh.[23] Therefore, when any of the latter definitions are used, the septal defect is not *intra*cristal but *infra*cristal. It is evident that disagreement in this respect is dependent upon nomenclature of the "crista supraventricularis" itself and embryologic theories regarding its origin. In order that the two should be distinguished, we believe that usage of the term "crista" should be restricted to a right ventricular structure of the *normal* heart until a standard nomenclature is adopted for application to supraventricular and septal muscle masses in malformed hearts. Until such a nomenclature is agreed upon, we believe that these muscular masses should be described in terms of their interpreted embryologic origin.

Spectrum of Anomalies Associated with "Lack of Conal Inversion"

Consideration of the developmental process outlined leads to the conclusion that Fallot's tetralogy should not be regarded as a well defined entity. Van Mierop and Wiglesworth[5] indicated the transition that exists from Eisenmenger complex (defined as ventricular septal defect with aortic dextroposition) to Fallot's tetralogy, and this view was endorsed by Goor et al.[7] Both anomalies are linked by the "lack of embryonic conal inversion," whereas the difference between them is produced by anterior deviation of the conal septum. Greater degrees of this anterior deviation would result in the anomaly of "pseudo-truncus arteriosus" or extreme tetralogy of Fallot, whereas lesser degrees of "lack of conal inversion" with normal septation would result in simple isolated ventricular septal defects. Similarly, greater degrees of "lack of conal inversion" will lead to the anomalous condition generally referred to as double outlet right ventricle, as indicated by the recent studies of Goor and Edwards[26] and Anderson et al.[27] (Fig. 13).

Acknowledgment

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Potassium Canrenoate in the Treatment of Long-Term Digoxin-Induced Arrhythmias in Conscious Dogs

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The effects of potassium canrenoate on arrhythmias induced by long-term progressive digoxin toxicity were studied in eight conscious beagle dogs. Sinus bradycardia and sinoatrial block, as well as atrioventricular (A-V) conduction disturbances, were consistently alleviated by administration of potassium canrenoate. Premature supraventricular (including junctional) and ventricular depolarizations as well as ventricular tachycardias were also suppressed. Although potassium canrenoate always terminated the digitalis-induced arrhythmias, it usually converted the rhythm to sinus arrhythmia rather than to normal sinus rhythm. Equimolar sodium canrenoate, but not potassium chloride, had similar reversal effects on arrhythmias induced by long-term digoxin intoxication. These data indicate that canrenoate, a diuretic agent with reported positive inotropic effects, may be useful in the treatment of digitalis-induced arrhythmias in man.

Arrhythmias secondary to digitalis toxicity continue to be a significant problem in clinical practice. Digitalis intoxication occurs in 8 to 20 percent[1–3] of hospitalized patients receiving digitalis, and the mortality rate directly attributable to such toxicity is 3 to 21 percent.[4–6] In addition to withdrawal of digitalis and the adjustment of electrolyte imbalance, corrective therapeutic regimens also embrace the use of available antiarrhythmic agents and electrical pacing, depending on the type of arrhythmia produced.

Most of the antiarrhythmic agents currently used to treat patients with digitalis toxicity produce undesirable side effects—depression of myocardial contractility, suppression of normal physiologic impulse formation or further depression of impulse conduction allowing the development or perpetuation of reentrant arrhythmias.[7–12] Recently, potassium canrenoate [potassium 3-(3-oxo-17β hydroxy-4, 6 androstadien-17α-yl)propanoate] or Soldactone®,* a newly synthesized specific antagonist of aldosterone, was introduced as a diuretic agent.[13,14] Potassium canrenoate is a steroidal compound and an open lactone analog of spironolactone [3-(3-oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)propionic acid-γlactone]. The diuretic and natriuretic potency of potassium canrenoate is said to be comparable to that of the thiazides.[13,14] In contrast to most antiarrhythmic agents, potassium canrenoate has been reported to have a positive inotropic effect in man and in isolated myocardial strips.[15,16] More significantly, this compound specifically antagonizes the toxicity of ouabain both in intact animals and in ventricular muscle-Purkinje fiber preparations.[17–20] Consequently, we studied the efficacy of canrenoate in long-term digoxin-induced cardiac arrhythmias in conscious dogs.[21]

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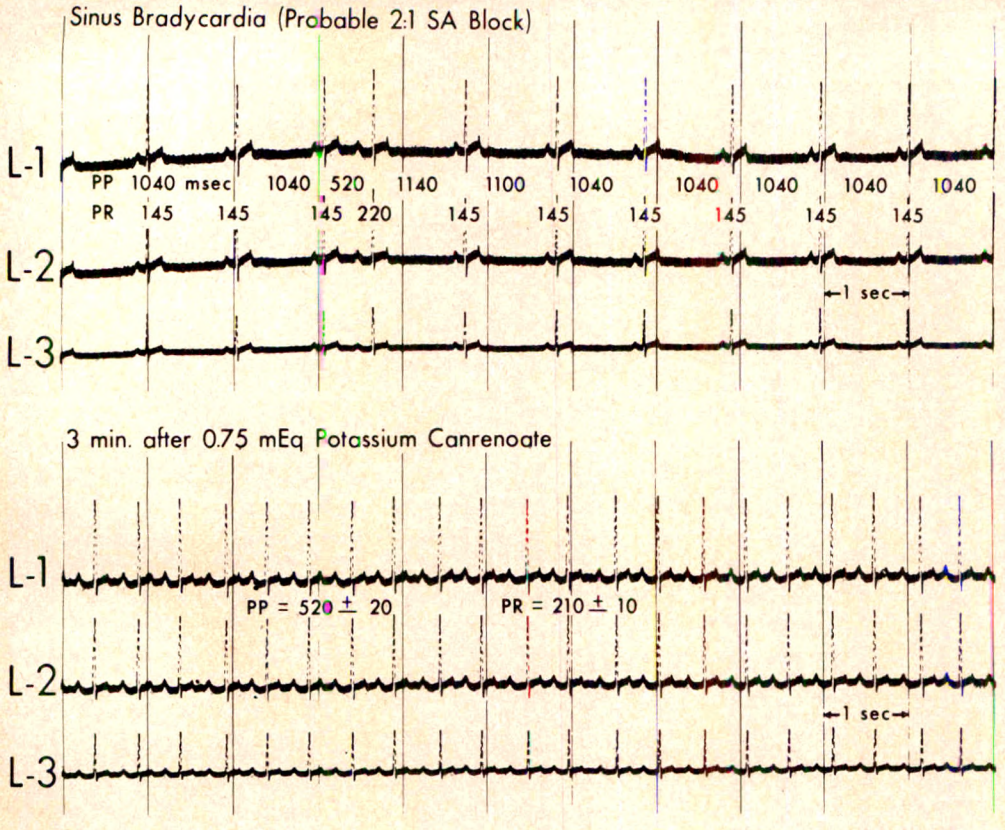


FIGURE 1. Dog 2. The effect of potassium canrenoate in a case of digoxin-induced sinus bradycardia (probable 2:1 sinoatrial [S-A] block). The predominant P-P interval before therapy **(upper panel)** was 1,040 msec, which is a multiple of 520 msec seen in one cycle, thus suggesting a likely diagnosis of 2:1 S-A block. Atrial rate was about 58/min before therapy. Within 3 minutes after administration of a total dose of 300 mg (0.75 mEq) of potassium canrenoate **(lower panel),** the atrial rate had doubled. The values for P-P and P-R intervals are in milliseconds. L-1, L-2 and L-3 = leads I, II and III, respectively.

TABLE I

Effects of Canrenoate Therapy on Arrhythmias Induced by Long-term Digoxin Toxicity in Conscious Dogs

Arrhythmia	Cases (no.)	Canrenoate Preparation	Average Dose (mg)	Responses
Sinus bradycardia (less than 60/min)	3	K	250	Restoration of sinus rhythm (100 to 120/min)
S-A block	1	K	300	Sinus rhythm (116/min)
Frequent premature atrial and junctional depolarizations (more than 12/min)	2	K	200	Suppression of premature supraventricular depolarizations; increased sinus rate to 150/min
A-V block				
A-V Wenckebach	7	K (5 cases); Na (2 cases)	300	1:1 A-V conduction; increased sinus rate
2:1, 3:1 A-V block and A-V dissociation	4	K (2 cases); Na (2 cases)	350	1:1 A-V conduction; increased sinus rate
Mobitz type II	1	K	200	Restoration of 1:1 A-V conduction; slightly increased sinus rate
Premature ventricular depolarizations (more than 12/min)	3	K (2 cases); Na (1 case)	200	Suppression of premature ventricular depolarizations with increased sinus rate
Ventricular tachycardia	2	K (1 case); Na (1 case)	200	Suppression of ventricular tachycardia with increased sinus rate
Bidirectional ventricular tachycardia	1	K	400	Restoration of sinus rhythm with improved intraventricular conduction

A-V = atrioventricular; K = potassium; Na = sodium; S-A = sinoatrial.

Material and Methods

Eight beagle dogs (3 male and 5 female) weighing 10 to 14 kg were trained to undergo electrocardiographic recordings, intravenous infusion and blood withdrawal. When training was judged adequate, electrocardiograms including the six standard limb leads and lead II rhythm strips were obtained twice a day for an observation period of at least 1 week. No animal manifested cardiac arrhythmia (except sinus arrhythmia, which is physiologic in conscious dogs) during this peiod. The animals were subsequently given a daily intramuscular injection of digoxin (0.0125 mg/kg per day). In some instances, two injections of digoxin were given in 1 day at 8 hour intervals. Electrocardiograms were obtained every day before and 30, 60 and 90 minutes after administration of each dose of digoxin. Cardiac arrhythmias secondary to digoxin toxicity generally developed within 7 to 10 days of this regimen.

When an arrhythmia was observed, the effect of the intravenous administration of canrenoate was evaluated. The animals continued to receive daily injections of digoxin whether or not they were studied to determine the effects of canrenoate. Potassium or sodium canrenoate was administered intravenously in a dose of 100 mg every 10 minutes, but not in excess of a total dose of 400 mg, until satisfactory conversion of the arrhythmia occurred. The electrocardiograms were monitored continuously during and after administration of canrenoate. Every 100 mg of potassium canrenoate contains 0.25 mEq (or millimole) of potassium (molecular weight of potassium canrenoate = 396.55). In the first part of the study, the effects of the diluents (D_5W) containing equivalent amounts of potassium chloride (up to 1 mM) were used as control injections 1 hour before potassium canrenoate therapy. Sodium canrenoate was used instead of potassium canrenoate in the latter part of the study. In the course of induced digoxin toxicity, each animal was studied three to four times at intervals of at least 2 days.

His bundle electrograms were obtained in three cases of arrhythmia observed in two dogs. One ml of 1 percent lidocaine was used for local infiltration anesthesia. By sterile technique, a small incision was made at the base of the left leg. After adequate exposure of the saphenous vein, a tripolar electrode catheter was inserted and advanced toward the medial cusp of the tricuspid valve until a stable recording of the His bundle electrograms was obtained.

Results

A total of 24 instances of cardiac arrhythmia secondary to progressive digoxin toxicity were recorded. In 18 cases, the animals were treated with potassium canrenoate; in the remaining 6 cases they were treated with sodium canrenoate. Twelve animals that received potassium canrenoate were given the diluent D_5W with an equivalent amount of potassium chloride as a control injection. These control injections had no significant effect on the arrhythmias.

In the conscious dogs with long-term digoxin intoxication, canrenoate generally increased the sinus rate, consistently improved atrioventricular (A-V) conduction and suppressed premature supraventricular (including junctional) and ventricular depolarizations and ventricular tachycardias. The average dose of canrenoate used for satisfactory conversion was 250 mg (0.625 mM) intravenously. The beneficial effects induced by each injection were evident within 2 minutes and were maintained for at least 60 to 90 minutes. With intravenous doses greater than 300 mg, retching and vomiting occurred in 30 percent of the animals studied. These symptoms were particularly evident when the drug was injected rapidly.

Table I summarizes the types of arrhythmia observed, the average doses of potassium and sodium canrenoate administered and the responses of the animals.

Sinus bradycardia: Three instances of sinus bradycardia without concomitant arrhythmias were observed in two dogs. One of these animals exhibited the same type of arrhythmia on two occasions within an interval of 48 hours. Sinus bradycardia was readily converted to normal sinus rhythm at a rate of 100 to 120/min with 1:1 A-V conduction. In another dog probable 2:1 sinoatrial block was successfully converted to regular sinus rhythm after administration of 300 mg of potassium canrenoate (Fig. 1).

A-V block: Disturbances in A-V conduction, seen frequently with digoxin toxicity, were observed in all eight animals. There were 12 recorded episodes of second degree A-V block (Fig. 2 to 5). First degree A-V block observed before development of second degree block was considered an effect of digoxin but not a result of toxicity. Canrenoate improved conduction in the A-V node, restoring 1:1 A-V conduction in all cases. Graded responses to increasing doses of canrenoate were readily demonstrable in dogs with these arrhythmias (Fig. 2). Most of the conversions were accompanied by increases (+20 to +50/min) in sinus rate in proportion to the total amount of drug administered. A-V dissociation with junctional tachycardia was also abolished and A-V conduction improved after treatment with canrenoate.

Ventricular arrhythmias: Digoxin-induced premature supraventricular and ventricular depolarizations occurring at a rate of more than 12/min were consistently suppressed by canrenoate. The upper panel in Figure 6 shows His bundle electrograms and surface electrocardiograms recorded simultaneously in a dog with digoxin-induced "slow" ventricular tachycardia. A ventricular focus was established because no His bundle potential preceded the ventricular depolarization. This animal was initially treated with potassium canrenoate (Fig. 6), and successful conversion to sinus rhythm with 1:1 A-V conduction was accomplished. After 90 minutes, the arrhythmia reverted to ventricular tachycardia. The animal was then given the same dose of sodium canrenoate and a similar conversion to sinus rhythm was obtained.

An advanced case of digoxin toxicity with "life-threatening" bidirectional ventricular tachycardia was observed on the 25th day of digoxin administration in one dog. The probability that this dog had a junctional tachycardia with alternating anterior and posterior hemiblock in the presence of right bundle

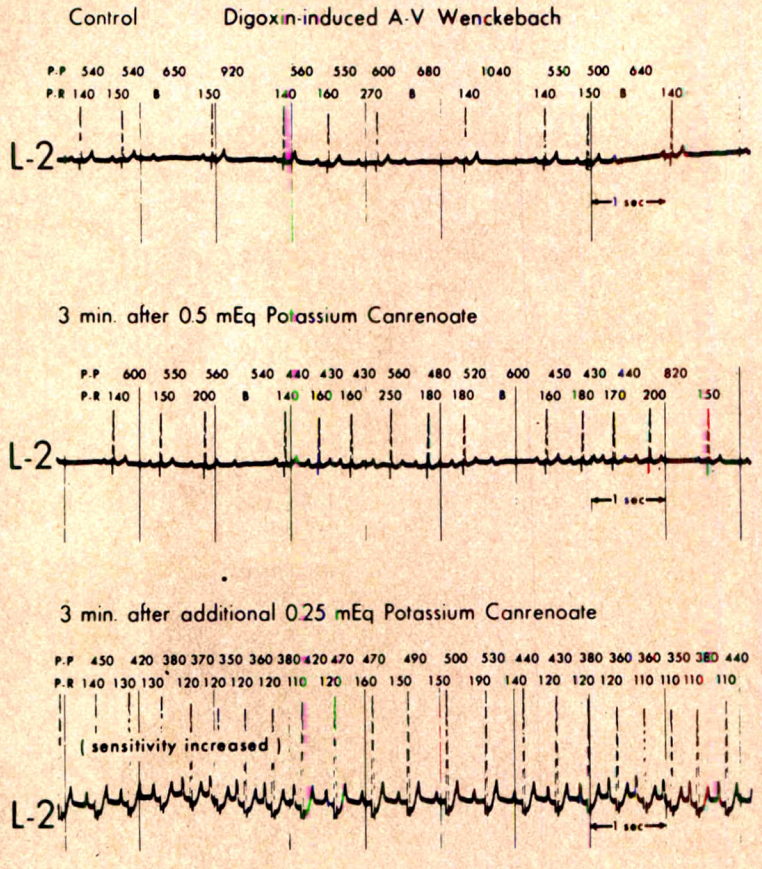


FIGURE 2. Dog 1. Step-wise responses to two succeeding doses of potassium canrenoate (injected at 10 minute intervals) in a case of digoxin-induced A-V block. The P-P and P-R intervals are as indicated (in milliseconds). "B" in **upper and middle panels** denotes blocked P waves in Wenckebach cycles. There was an increase in sinus rate with a longer Wenckebach cycle after a total dose of 200 mg (0.5 mEq) of potassium canrenoate **(middle panel).** An additional dose of 100 mg (0.25 mEq) caused a further improvement in sinoatrial activity and conversion to 1:1 A-V conduction **(lower panel).**

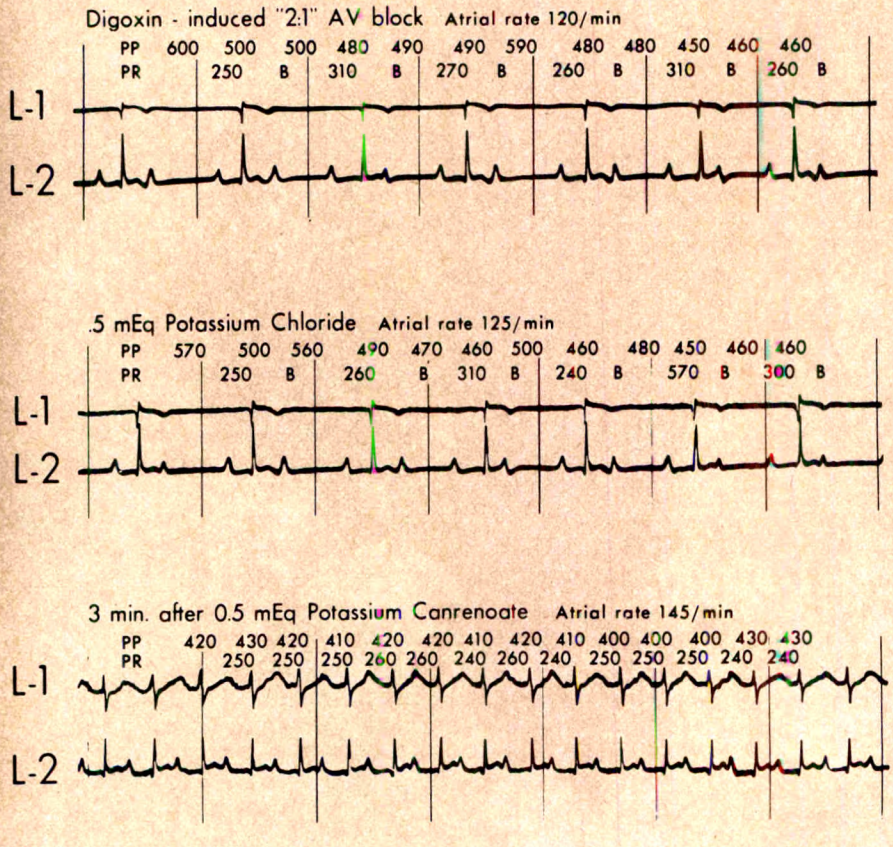
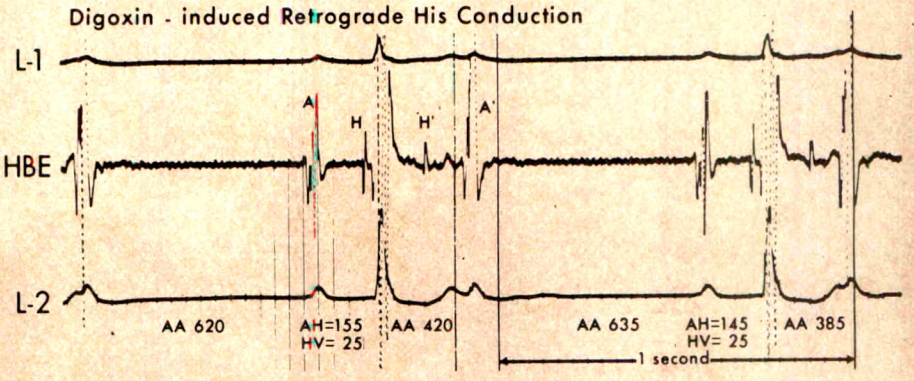


FIGURE 3. Dog 6. The effects of equimolar amounts of potassium chloride and potassium canrenoate in digoxin-induced 2:1 A-V block **(upper panel).** The enhancement of sinoatrial activity and restoration of 1:1 conduction with a prolonged P-R interval was induced by an injection of potassium canrenoate **(lower panel)** but not potassium chloride **(middle panel).** Note the persistence of sinus arrhythmia after treatment with canrenoate. The more normal appearance of the QRS pattern in lead I **(lower panel)** suggests a possible improvement in intraventricular conduction after canrenoate therapy.



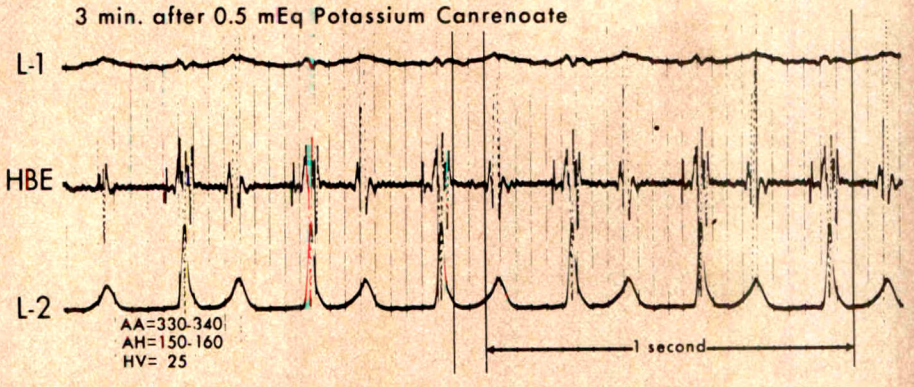


FIGURE 4. Dog 5. His bundle electrograms (HBE) in a case of second degree A-V block with retrograde His bundle reentry and 2:1 A-V block **(upper panel).** It is possible that the atrial depolarization after the His bundle potential conducted in retrograde fashion represents an atrial echo that was blocked in antegrade manner. A more likely interpretation would be a 2:1 A-V block with ventriculophasic sinoatrial arrhythmia; the His potential (H′), activated in retrograde fashion, failed to propagate to the atrium. Transformation of the second degree A-V block to first degree A-V block was accomplished after a 200 mg (0.5 mEq) intravenous dose of potassium canrenoate, even though the sinus rate had increased **(lower panel).**

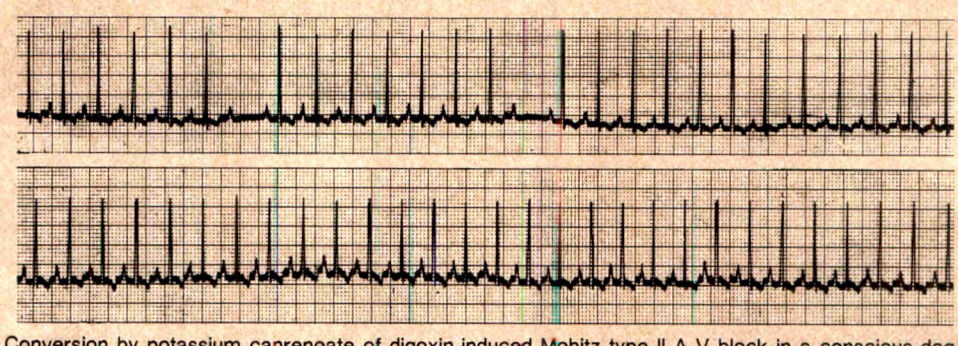


FIGURE 5. Dog 4. Conversion by potassium canrenoate of digoxin-induced Mobitz type II A-V block in a conscious dog. (Lead II tracings are shown.) Mobitz type II block occurred 18 days after daily intramuscular administration of digoxin, 0.0125 mg/kg **(upper panel).** Within 3 minutes after an intravenous injection of potassium canrenoate, 0.5 mEq, 1:1 conduction was restored **(lower panel).**

branch block cannot be ruled out. However, the QRS axis in three simultaneously recorded frontal leads (Fig. 7) failed to elucidate determinable axis deviations in the frontal plane. Administration of potassium canrenoate converted this arrhythmia to regular sinus rhythm with 1:1 A-V conduction. A more normal-appearing QRS interval with shortened duration was noted after the conversion.

Measurements in three dogs with ventricular tachycardia revealed that serum digoxin levels were greater than 5 ng/ml.

Discussion

Recent studies in anesthetized dogs have shown that a simultaneous infusion of potassium canrenoate and ouabain produces a significant delay in the onset of ouabain-induced ventricular tachycardia.[17,18] Ventricular bigeminy and ventricular tachycardia induced by ouabain have also been successfully converted by potassium canrenoate.[17,18] Our unpublished data showed that potassium canrenoate suppressed ventricular arrhythmias induced by ouabain in anesthetized dogs with complete heart block due to injection of formalin into the area of the A-V node. Thus, the antiarrhythmic activity of potassium canrenoate can be demonstrated in vivo in the absence of conducted supraventricular impulses. This finding indicates that the "sinus overdrive" mechanism need not be postulated as an in vivo antiarrhythmic mechanism of potassium canrenoate.

The specificity of this substance in relation to the toxic manifestations of cardiac glycosides has been demonstrated in vivo[19] and in vitro.[20] Potassium canrenoate was ineffective in arrhythmias not induced by digitalis toxicity and apparently did not affect the alpha and beta adrenergic receptors.[19] Our unpublished data showed that blood pressure responses to potassium canrenoate ranged from a mild vasodilation to a mild vasoconstriction in normal control dogs. It is therefore unlikely that the actions of canrenoate are mainly mediated by catecholamines. Potassium canrenoate has also been shown to have no

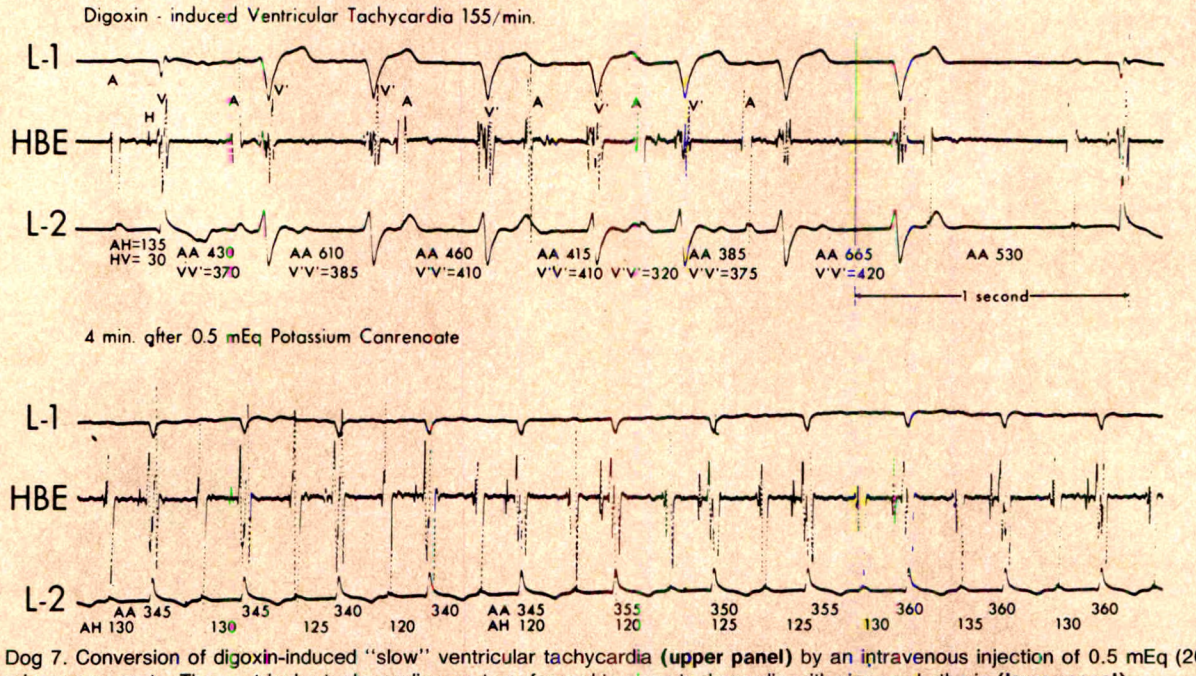


FIGURE 6. Dog 7. Conversion of digoxin-induced "slow" ventricular tachycardia **(upper panel)** by an intravenous injection of 0.5 mEq (200 mg) of potassium canrenoate. The ventricular tachycardia was transformed to sinus tachycardia with sinus arrhythmia **(lower panel).**

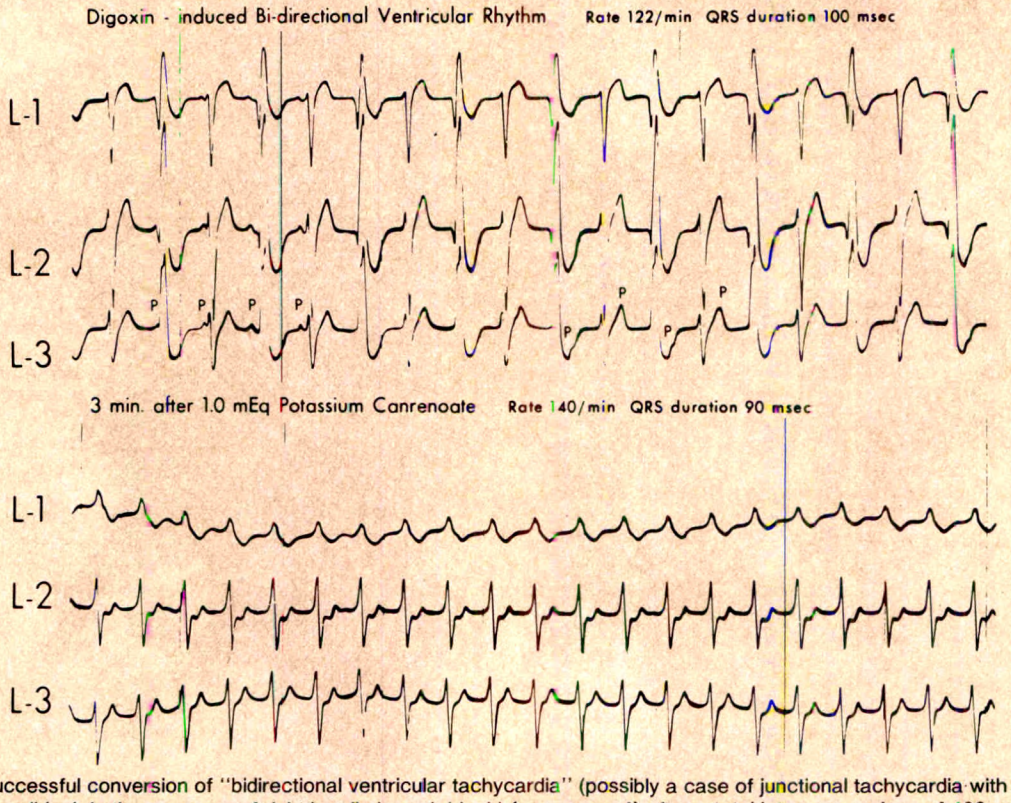


FIGURE 7. Dog 3. Successful conversion of "bidirectional ventricular tachycardia" (possibly a case of junctional tachycardia with alternating anterior and posterior hemiblock in the presence of right bundle branch block) **(upper panel)** after a total intravenous dose of 400 mg of potassium canrenoate. The duration of the QRS interval **(lower panel)** decreased after conversion even though the heart rate was faster than in the control tracing.

effect on Purkinje fibers damaged by stretch and hypoxia and to be almost inert in its action on normal Purkinje fibers in concentrations up to 10 times greater than the effective concentration for digitalis toxicity.[20]

Our previous studies of ouabain-induced arrhythmias were performed in dogs anesthetized with sodium pentobarbital. Because of the vagolytic action of pentobarbital, the sinus rate was rapid and A-V conduction was maximally facilitated. Only ventricular arrhythmias could be induced by an acute infusion of ouabain under these circumstances. In this study we investigated the effects of canrenoate in arrhythmias induced by long-term digoxin intoxication in conscious dogs because such arrhythmias closely resemble those seen in clinical settings. As in man, sinus bradycardia, sinoatrial arrest, various types of A-V block, enhanced junctional automaticity and ventricular arrhythmias were induced by digoxin in our conscious dogs. An incidental finding was that premature atrial depolarizations, observed relatively rarely in man, frequently occurred in our dogs during the course of digoxin intoxication.

Mechanism of reversal of digitalis toxicity by canrenoate: The molecular structure of canrenoate bears a resemblance to that of digitalis so that competitive inhibition of cardiac glycoside offers an interesting possible explanation of the salutory effects of potassium canrenoate in digitalis toxicity. Like digitalis compounds, canrenoate given in bolus injections also caused retching and vomiting, a finding that may signify stimulation of the chemoreceptor trigger zone described by Borison and Wang.[22]

Stimulation of drug-metabolizing enzymes cannot explain the rapid onset of the effects of canrenoate in the animal studies nor the efficacy of the drug in reversing the electrophysiologic effects of ouabain toxicity in isolated canine Purkinje fibers. Baskin et al.[23] have recently shown that potassium canrenoate failed to reverse the ouabain effect on sodium-potassium-adenosine triphosphatase preparations from guinea pig heart or rat brain.[23] A possible mechanism of the effects of canrenoate in reversing digitalis toxicity is the competitive displacement of digitalis by canrenoate from membrane sites and consequent improvement in cation fluxes, since canrenoate has also been observed to inhibit adenosine triphosphatase activity and rubidium uptake by erythrocytes.[24] Similar drug activity has been either postulated or demonstrated for triamterene and amiloride, two potassium-sparing diuretic agents that are capable of reversing digitalis intoxication.[25,26]

Clinical implications: This study of conscious dogs with long-term digitalis toxicity induced by digoxin rather than ouabain lends further strong support for the efficacy of canrenoate in the treatment of clinical arrhythmias due to digitalis toxicity. Our data suggest that potassium canrenoate is effective in suppressing arrhythmias due to digitalis-induced conduction block and enhanced ectopic automaticity but does not appear to be effective against sinus arrhythmias in conscious digitalis-intoxicated dogs. The latter finding may be partially due to a physiologic phasic change in vagal tone in the sinoatrial node that is augmented by digitalis compounds. Thus, one usually finds sinus rhythm with sinus arrhythmia in a digitalis-intoxicated dog treated with potassium canrenoate for a more serious rhythm disturbance due to digitalis intoxication. Our data suggest that the antiarrhythmic effect of potassium canrenoate is not related to the potassium in its molecule.

Acknowledgment

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Pathophysiology of Second Degree Atrioventricular Block: A Unified Hypothesis

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An in vivo and in vitro correlative study of second degree atrioventricular (A-V) block in the canine proximal His-Purkinje system after ligation of the anterior septal artery is reported. Evidence is presented to suggest that Mobitz type II and the Wenckebach type of conduction represent different degrees of the same disorder rather than two distinct electrophysiologic processes. The in vivo study showed that an increment of conduction delay almost always preceded the blocked impulse in second degree A-V block. The increment, as small as 1 or 2 msec at the early stage of block, often increased gradually up to 180 msec. The in vitro study consistently showed an increment of conduction delay preceding the blocked impulse. The same experiments revealed a greater increment in conduction delay early after excision that, on recovery during superfusion, gradually decreased to a few milliseconds (the reverse order of the in vivo observation). Characteristic changes in duration and configuration of action potentials in the ischemic proximal His-Purkinje system were observed depending on the state of transmission and the temporal relation of the impaled cell to areas of slow propagation and block. The study revealed a remarkable similarity between characteristics of conduction in the ischemic His-Purkinje system and conduction in both the normal A-V node and Purkinje fibers subjected to various pathophysiologic interventions.

It is suggested that in the pathologic situation—exemplified in this study by acute myocardial ischemia—the normal His-Purkinje system may gradually lose the characteristics of the fast response and start showing properties of the slow response. At an early stage of departure from normal, the proximal His-Purkinje system may show second degree A-V block with no perceptible to a few milliseconds' increment of conduction delay (the equivalent of Mobitz type II block). On further departure from normal, the His-Purkinje system resembles the A-V node in showing a significant increment of conduction delay prior to the blocked impulse (the equivalent of Wenckebach periodicity). Both the in vivo and in vitro observations demonstrated a clear propensity of the ischemic proximal His-Purkinje system to develop paroxysmal A-V block during the stage of second degree A-V block when there is no perceptible to a few milliseconds' increment of conduction delay. A new classification of second degree A-V block is presented based on the suggested electrophysiologic mechanism.

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Two types of second degree atrioventricular (A-V) block were originally described by Wenckebach[1,2] and Hay[3] from analysis of the *a-c* interval of the jugular pulse. After the introduction of the electrocardiogram these were classified by Mobitz[4] as types I and II. Type I A-V block, also known as Mobitz type I or the Wenckebach phenomenon, is defined as intermittent failure of A-V conduction preceded by progressive lengthening of A-V conduction times. Type II A-V block, also known as Mobitz type II block, is characterized by inter-

mittent failure of A-V conduction that occurs "suddenly" and in which the P-R intervals remain constant before the dropped beat. During three successive eras, beginning with deductive analysis of standard electrocardiograms, followed by electrophysiologic studies utilizing the microelectrode technique and the more recent catheter electrode technique, the classification of second degree A-V block into two types has been maintained. Emphasis was recently placed on specific localization of each type in the A-V conduction system with less attention directed to unraveling the basic electrophysiologic mechanisms involved. This is especially so for Mobitz type II A-V block, which is still considered by some an electrophysiologic curiosity.

We recently produced an appropriate experimental model for study of A-V conduction disorders after ligation of the anterior septal artery in the dog.[5–9] Ligation of the artery gives rise to acute ischemic injury of the proximal His-Purkinje system. This model offers a unique opportunity to analyze the evolution of second degree A-V block. Evidence has been accumulated during these studies to suggest that Mobitz type II and the Wenckebach type of second degree A-V block represent different degrees of the same disorder rather than two different electrophysiologic processes. We conducted in vitro studies utilizing the same experimental model and obtained correlative evidence to the in vivo observations.[10–12] On the basis of both the in vivo and in vitro data, a unified hypothesis to explain second degree A-V block is presented.

Material and Methods

Forty-five adult mongrel dogs weighing 10 to 20 kg were anesthetized with intravenously administered sodium pentobarbital (30 mg/kg body weight). The animals were intubated and placed on a mechanical respirator. Blood pressure in the femoral artery was monitored through a polyethylene catheter connected to a Statham transducer. A thoracotomy was performed through the fourth left intercostal space. The bifurcation of the left coronary artery was exposed by retracting the tip of the left atrial appendage and incising the epicardium overlying the proximal portions of the anterior descending and left circumflex coronary arteries. The anterior septal artery was exposed by blunt dissection of the bifurcation and branches of the left coronary artery, and a silk ligature was placed around the vessel to be occluded after control records were taken. To increase the heart rate, atrial pacing by means of a bipolar plunge wire electrode (diameter 0.003 inch) inserted at the left atrial appendage was utilized. Pacing was performed with a Grass S-88 stimulator and SIU5 stimulus isolation unit. Vagal-induced slowing or cardiac arrest was accomplished by delivery of 0.05 msec square wave pulses of 1 to 20 volts intensity at a frequency of 20 hertz through silver electrodes (diameter 0.012 inch) inserted into the left or right cervical vagosympathetic trunk.[13]

Recordings from the specialized ventricular conducting tissue and regular ventricular muscle were obtained by electrode catheters inserted into peripheral arteries and veins[14,15]; into the left or right common carotid artery to the aortic root for recording His bundle activation; into a femoral artery to the left ventricle to record from the proximal or distal left bundle branch; and into a femoral vein to the right heart to record from the His bundle at the A-V junction on the right side or the right bundle branch. In some cases after placement of the anterior septal ligature, the left thoracotomy was closed and the animal turned to expose the heart through a right thoracotomy. One to three pairs of plunge wire electrodes were placed in the His bundle area[16] and electrode catheters were inserted to record right and left bundle branch potentials. In addition to the electrograms two or more standard electrocardiographic leads were recorded, specifically leads II and aVR. To validate each of the catheter electrode and plunge wire recordings, pacing at various intensities, that is, just above threshold and two to three times threshold, was performed at various rates from each of the bipolar electrodes. In experiments in which an intra-His bundle lesion developed with the His bundle potential split into two deflections (H_1 and H_2), validation of both His deflections was carried out as previously described.[7]

All records were obtained on a multichannel oscilloscopic photographic recorder (E for M DR-8) at paper speeds of 25 to 200 mm/sec with filter frequencies of 0.1 to 200 hertz for electrocardiographic leads and 40 to 200 hertz for electrographic recordings. Calculations were accurate up to ±3 msec at a paper speed of 200 mm/sec. Some of the recordings were stored on a magnetic tape recorder (Honeywell 5600) and replayed so that selected sections could be registered on photographic paper for detailed analysis. Control records during sinus rhythm, vagal-induced cardiac slowing and atrial pacing up to rates that produced A-V Wenckebach conduction were obtained in each experiment before the anterior septal artery was ligated. The recorded electrical activity was then monitored for intervals up to 8 hours after ligation. In all experiments postmortem dissection was performed to verify that the anterior septal artery had been completely occluded.

In vitro studies were carried out in 15 hearts in which the anterior septal artery had been ligated and in vivo observations for 3 to 8 hours had shown the development of various degrees of conduction disorders in the proximal His-Purkinje system. In addition, 10 noninfarcted hearts were also studied as controls. A modified Elizari preparation[17] was utilized to expose the proximal A-V conduction system. In both ischemic and control experiments, the heart was rapidly excised and immersed in cool, oxygenated Tyrode solution. The right and left ventricles were opened from base to apex and most of the free walls was removed. The A-V valve leaflets and chordae tendineae were rapidly cut away close to their septal insertion on both the right and left sides. The atria were removed except for the basal portions containing the A-V node and His bundle. This atrial and ventricular septal preparation was placed on a plastic plate with the left side down and, with use of a sharp no. 21 scalpel blade, one single straight-line incision was made from the mouth of the coronary sinus to just outside the origin of the right bundle branch. In this way the atrial septum was transsected, exposing the penetrating and branching portions of the His bundle. The interventricular septum was then divided into right and left sides by splitting it down the center working from apex to base. This resulted in a flat relatively two-dimensional preparation of the top of the ventricular septum containing the His bundle and the right and left ventricular septum containing their respective proximal and distal bundle branches. The entire preparation was pinned in a lucite chamber with an approximate volume capacity of 60 ml and superfused

with warmed (35 to 37° C) and gassed (95 percent oxygen, 5 percent carbon dioxide) solution of the following millimolar composition: sodium ion 151.1; potassium ion 4.05; calcium ion 1.35; magnesium ion 0.5; chlorine ion 131.25; bicarbonate radical 24.0; dibasic phosphate radical 1.8; dextrose 5.5.

Extracellular and intracellular potentials were recorded from the penetrating and branching portions of His as well as from the right and left bundle branches. The penetrating and branching portions of the bundle of His were identified grossly by anatomic landmarks.[17] Extracellular potentials were recorded with bipolar electrodes of Teflon-coated stainless steel wires (diameter 0.003 inch) led into differential operational amplifiers. Intracellular potentials were recorded with machine-pulled microelectrodes with tip resistance of 10 to 40 megohms when filled by boiling with 3 molar potassium chloride. The microelectrodes were connected through a silver-silver chloride interface to the input of a high impedance (greater than 10^{12} ohms) amplifier of low gain (3×) and adjustable negative capacitance (Bioelectric NF1). The indifferent electrode in the chamber was an agar bridge of 3 molar potassium chloride with a silver-silver chloride interface. The outputs of the first stage amplifiers were led into a plug-in amplifier (Tektronix 3A74) in a dual beam oscilloscope (Tektronix 565). The preparation was stimulated by rectangular pulses delivered from wave form and pulse generators (Tektronix 160 series) through fine Teflon-coated bipolar silver wire electrodes. Voltage calibrations for intracellular recordings was accomplished by a calibrator voltage (100 mv) inserted across 100 ohms between the indifferent electrode and ground. The oscilloscopic tracings were photographed on 35 mm film (Grass C4N).

Results

In Vivo Observations

In all animals the control records showed a Wenckebach type second degree A-V block localized between recording sites of the atrial and His bundle deflections at pacing rates between 240 and 310/min. Neither the dissection of the anterior septal artery itself nor the placement of plunge wire electrode was accompanied by significant trauma to the A-V conduction system, as shown in control experiments.[7] All but 1 of the 39 dogs that survived the early arrhythmic period after ligation of the anterior septal artery subsequently manifested—within 1 to 2 1/2 hours of ligation—various degrees of conduction disorders at the level of the His bundle, right and left bundle branches or any combination thereof (Table I).

TABLE I

Localization of Conduction Disorders in the Canine Proximal His-Purkinje System After Ligation of the Anterior Septal Artery in 38 Experiments

Group	Experiments (no.)	Site of Conduction Disorder		
		His Bundle	Right Bundle	Left Bundle
I	2	−	+	−
II	10	+	−	−
III	12	+	+	−
	4	+	−	+
IV	8	−	+	+
V	2	+	+	+

Second degree A-V block in intra-His bundle lesion: The gradual evolution of second degree A-V block was more clearly illustrated when the conduction disorder was localized in the His bundle rather than in both bundle branches (bilateral bundle branch block). In case of an intra-His bundle lesion characteristic changes were observed in the recorded His bundle potential as well as the H-V interval.

Figure 1 illustrates a catheter electrode recording of the His bundle from the right side (Hb-R). The control recording (panel A) reveals a sharp His bundle spike with an H-V interval of 30 msec. Panels B to D, obtained 60, 75, and 90

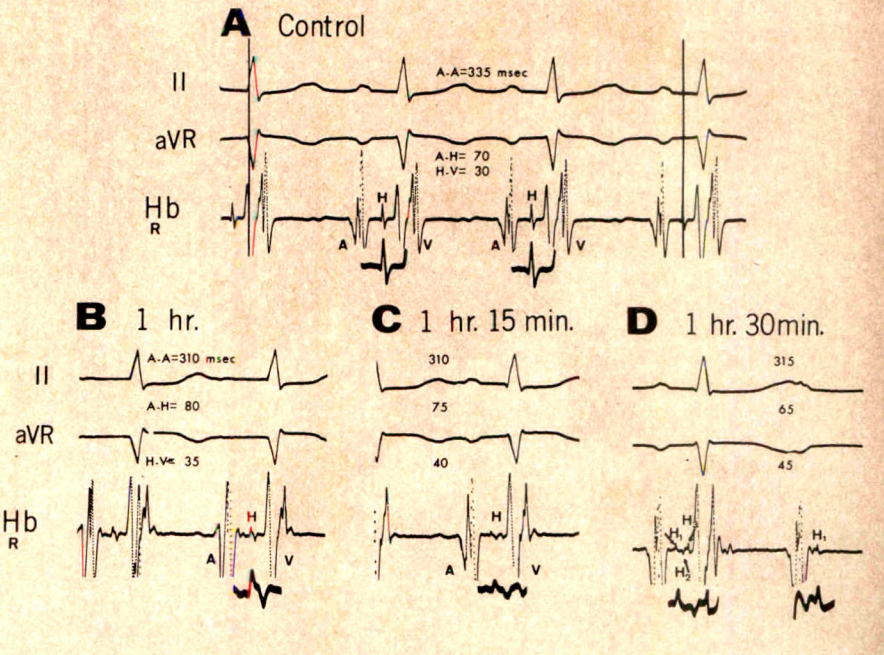

FIGURE 1. Catheter electrode recording of the His bundle from the right side (Hb-R) recorded simultaneously with leads II and aVR, showing evolution of intra-His bundle block. See text for details.

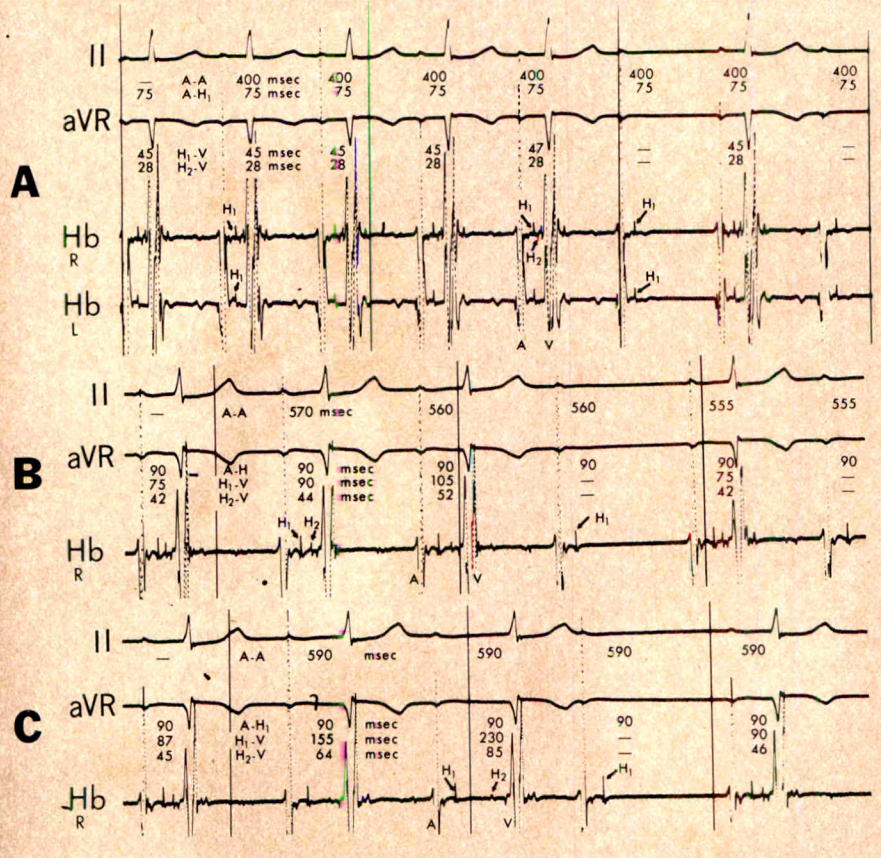

FIGURE 2. Record obtained from the same experiment as in Figure 1 showing characteristic evolution of second degree intra-His bundle block. See text for details. In this and subsequent figures, Hb-R and Hb-L represent catheter electrode recordings of the His bundle from the right and left sides of the heart, respectively. Time lines in this and subsequent figures are set at 1 second intervals.

minutes, respectively, after ligation of the anterior septal artery, illustrate the gradual fractionation of the His bundle potential that later split into three distinct deflections (H_1, H_2 and H_3) in panel D. This process was associated with a gradual increase in duration of the His bundle deflection and the H-V interval and represents first degree intra-His bundle block. Figure 1, panel D, shows the development of A-V block localized between the H_1 deflection on one side and the H_2-H_3 deflections on the other side.

Characteristic pattern of second degree intra-His bundle block: In most of the experiments showing an intra-His bundle lesion, the His bundle potential was usually split into two deflections (H_1 and H_2), and an increase of the H-V interval of 10 to 20 msec was observed before intermittent block of the impulse developed either spontaneously or in response to atrial pacing. A characteristic pattern was observed for the evolution of second degree intra-His bundle block. At early stages of the experiment, intra-His bundle block occurred with no perceptible increment of conduction delay. The P-R, H_1-V and H_1-H_2 intervals remained "constant" in the first conducted beat subsequent to and the last conducted beat prior to the blocked atrial impulse. This corresponded to the Mobitz type II block. Later in the experiments, the H_1-V interval lengthened gradually and the H_1-H_2 intervals showed a gradual increment before the blocked P wave. The increment, which is at first only a few milliseconds, may gradually increase up to 180 msec giving rise to an obvious Wenckebach periodicity in the electrocardiographic leads. The sequence of second degree intra-His bundle block is shown in Figure 2, which was obtained from the same experiment as Figure 1.

Figure 2, panel A, was recorded 100 minutes after ligation of the anterior septal artery and illustrates catheter electrode recordings of the His bundle potential from the right and left sides of the heart (Hb-R and Hb-L, respectively). The Hb-R recording illustrates a split His bundle deflection whereas the Hb-L recording depicts only the H_1 deflection.[7] The record shows second degree intra-His bundle block with essentially constant H_1-V and H_1-H_2 intervals in the last conducted beat prior to and in the first conducted beat subsequent to the blocked impulse. Panel B was obtained 60 minutes later and illustrates a gradual increment of the H_1-V interval of 30 msec before failure of ventricular response to the fourth atrial impulse. The gradual increment of conduction delay is mainly localized between the H_1-H_2 deflections where the final block of the impulse takes place. However, there are additional conduction delays at the site of recording of the H_2 deflection and between the H_2 and V deflections, as revealed by the decrease in amplitude and increase in the duration of the H_2 deflection as well as the increase in the H_2-V interval. Panel C, obtained 60 minutes after panel B, illustrates an obvious Wenckebach periodicity in the electrocardiographic leads. An increment of 143 msec in the H_1-V intervals is observed before block of the atrial impulse.

Wenckebach phenomenon: Typical Wenckebach periodicity[18] was not a common observation in the study. Several variations of the Wenckebach phenomenon were commonly observed. Two of these variations are shown in Figure 3.

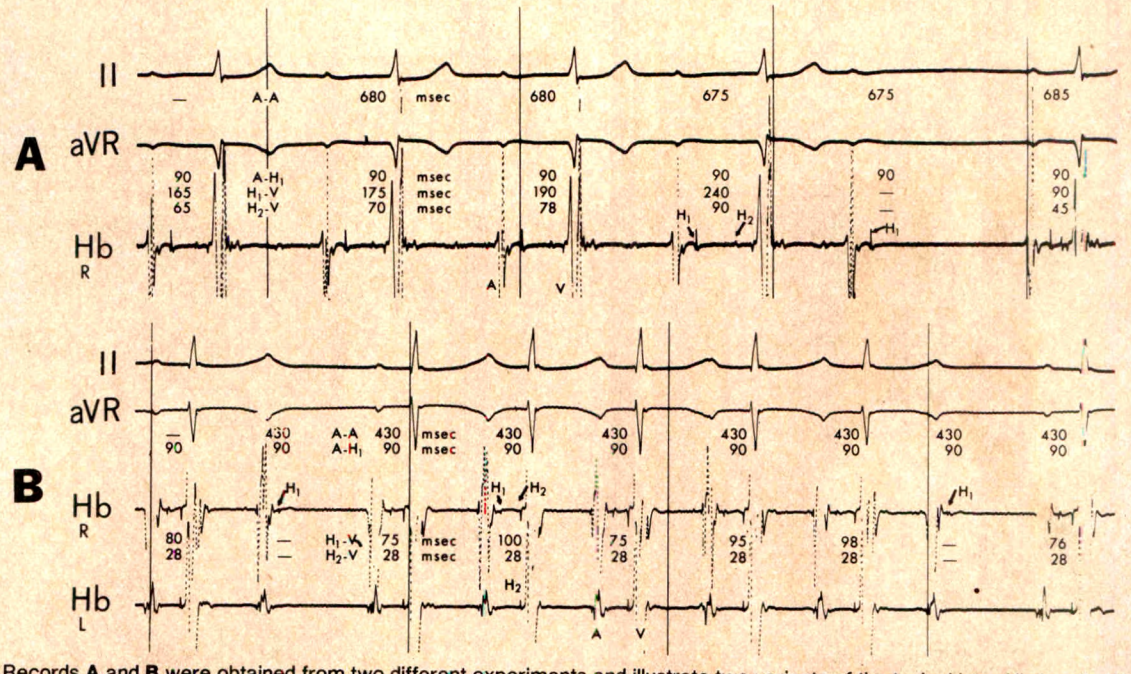

FIGURE 3. Records **A** and **B** were obtained from two different experiments and illustrate two variants of the typical intra-His bundle Wenckebach periodicity. See text for details.

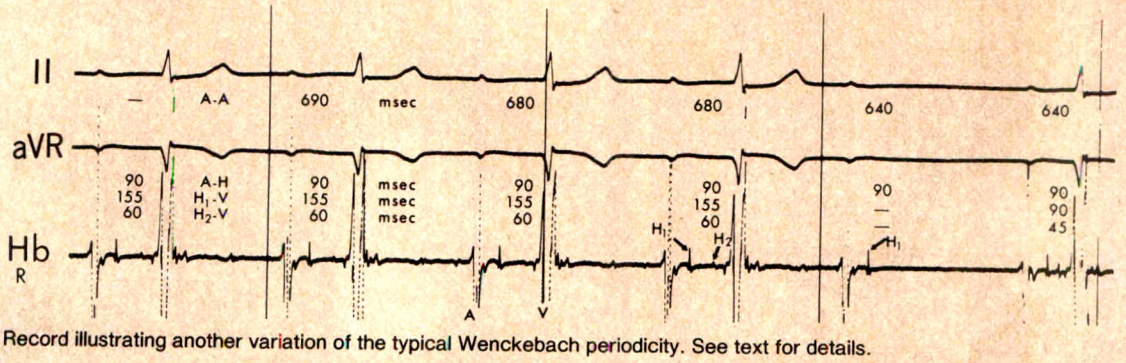

FIGURE 4. Record illustrating another variation of the typical Wenckebach periodicity. See text for details.

Figure 3, panel A, illustrates the last part of a long Wenckebach period. There are continual increments of the H_1-V interval of 15 msec; a larger increment of 50 msec is seen in the last conducted beat. These changes resulted in a gradual increase of the R-R intervals before the pause. Panel B, obtained from another experiment, illustrates catheter electrode recordings of the His bundle from the right and left sides of the heart (Hb-R and Hb-L, respectively). The record shows that the increment of the H_1-V interval was greatest in the second conducted beat of the Wenckebach cycle (from 75 to 100 msec). Shortening of the H_1-V interval of the third conducted beat to 75 msec then occurred, followed by a gradual increase of the H_1-V interval of the fourth and fifth conducted beats to 95 and 98 msec before the block.

Figure 4 shows another variation of the typical Wenckebach periodicity. The record illustrates an apparent Mobitz type II block when the criterion used is only the presence of constant P-R intervals prior to the blocked impulse rather than a constant P-R interval of the beats immediately preceding and immediately following the pause. The record shows constant prolonged H_1-V intervals of 155 msec with sudden intra-His bundle block of the fifth atrial impulse. The first conducted beat after the pause shows marked shortening of the H_1-V interval to 90 msec. This arrangement was occasionally seen in long Wenckebach periods in which the last conducted beats showed a prolonged and almost constant conduction time. The sudden block of the impulse sometimes coincided with minimal shortening of the P-P cycles.

Figure 4 demonstrates that the intra-His bundle block of the fifth atrial impulse coincided with a sudden shortening of the A-A cycle by 40 msec. In these cases the P-R interval of the first conducted beat after the pause was always shorter than the P-R interval of the last conducted beat in the Wenckebach period.

Paroxysmal A-V block: During the study a close temporal association was observed between the occurrence of early stages of second degree A-V block in the proximal His-Purkinje system and the induction or spontaneous onset of intermittent complete A-V block (paroxysmal A-V block). Paroxysmal A-V block was clearly tachycardia-dependent since block could be induced by atrial pacing at a critical heart rate

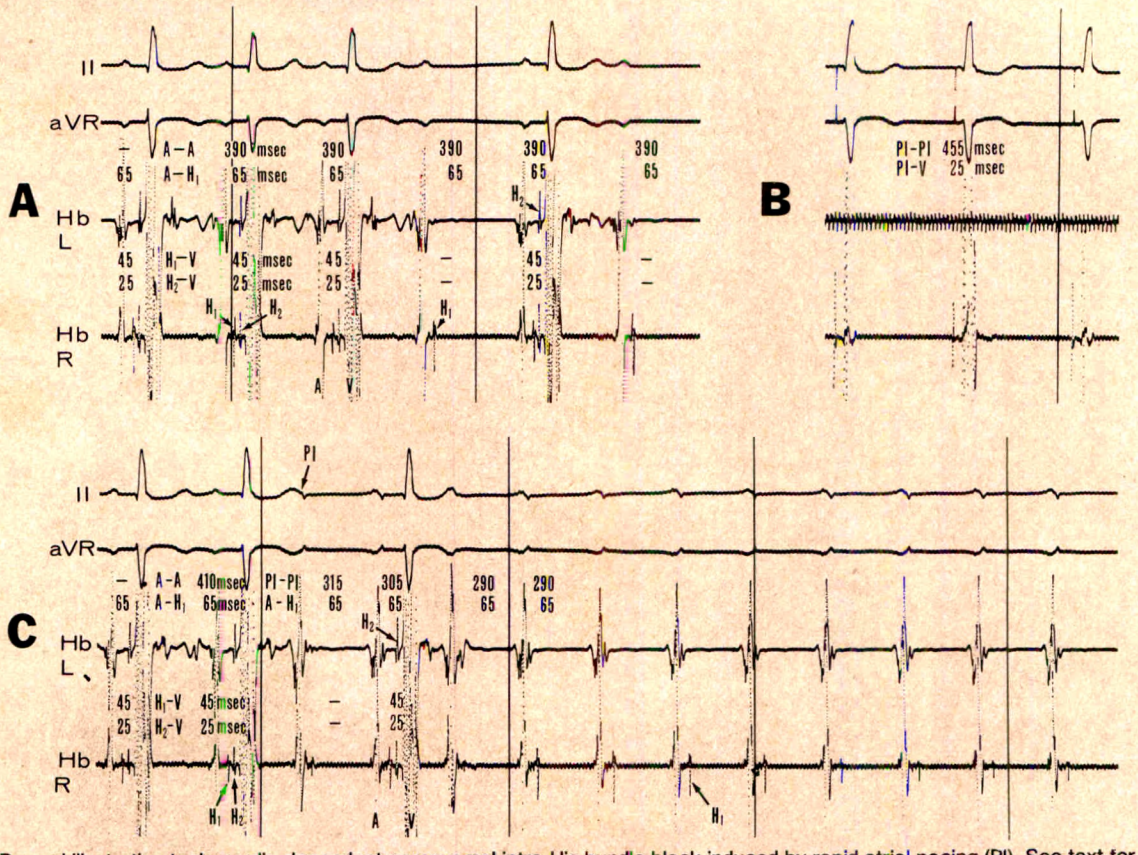

FIGURE 5. Record illustrating tachycardia-dependent paroxysmal intra-His bundle block induced by rapid atrial pacing (PI). See text for details.

(180 to 300/min in different experiments). This is shown in Figure 5.

Figure 5, panel A, was obtained 2 hours after ligation of the anterior septal artery and shows catheter electrode recordings from the left and right sides of the heart. The record illustrates a spontaneous Mobitz type II intra-His bundle block. Panel B shows distal His bundle pacing from the catheter electrode in the aortic root. Panel C was obtained 5 minutes later. The first two beats represent 1:1 A-V conduction at a rate of 153/min. Atrial pacing started at the third P wave (PI) with gradual increase of the pacing rate. A 2:1 intra-His bundle block developed and was followed by complete intra-His bundle block at a critical shortening of the atrial cycle length to 290 msec (rate 207/min).

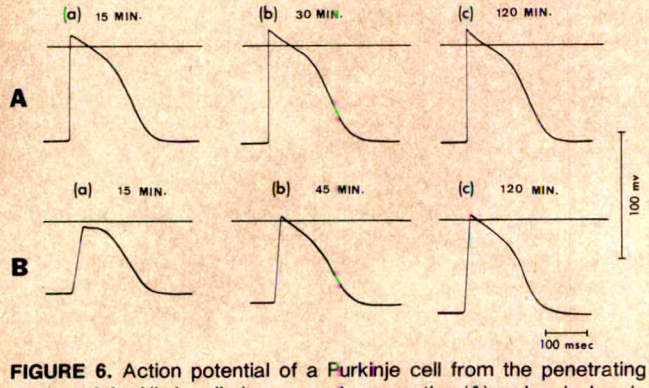

FIGURE 6. Action potential of a Purkinje cell from the penetrating portion of the His bundle in a normal preparation (**A**) and an ischemic preparation (**B**) recorded at different time intervals after excision. Note gradual recovery during superfusion in **B**. See text for details.

In Vitro Observations

Noninfarcted hearts: In 10 preparations from noninfarcted hearts, the action potentials recorded from the penetrating and the branching portions of the His bundle as well as from the proximal bundle branches were normal. In some preparations there was a slight increase in resting potential, upstroke velocity, amplitude and overshoot in time during superfusion (Fig. 6, panel A). This change probably indicated recovery of the cells from any slight damage suffered during the dissection. The mean resting potential of a His bundle Purkinje cell in 10 normal preparations was 72 mv (standard deviation ± 4), the mean action potential amplitude was 85 ± 9 mv, and the mean action potential duration at a driving cycle length of 800 to 1,000 msec was 220 ±20 msec. The mean conduction time from a proximal His bundle position to a proximal right or left bundle position was 16 ± 4 msec. His bundle cells were usually able to follow rapid driving at rates of 300/min or more.

Infarcted hearts: All the preparations from infarcted hearts manifested deviations from the electrophysiologic properties described above. Most of the altered cells were localized quite proximally in the His-Purkinje system. Intracellular recordings from Purkinje cells in the bundle of His and very proximal bundle branches revealed diminished resting and action potentials, reduced upstroke velocity and depressed excitability. In time, during superfusion, these cells underwent a process of recovery characterized by gain in amplitude of resting and action

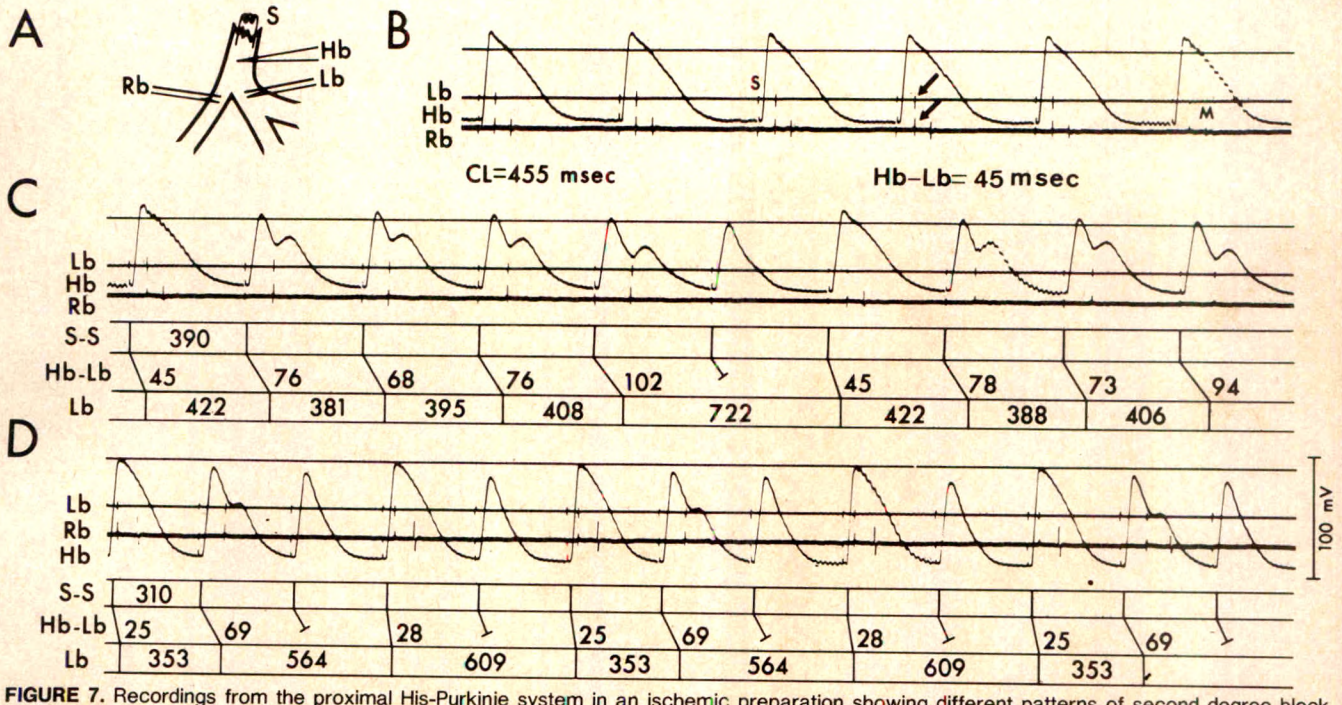

FIGURE 7. Recordings from the proximal His-Purkinje system in an ischemic preparation showing different patterns of second degree block. See text for details. The sketch in **A** shows the arrangement of the stimulating and recording electrodes. The preparation was stimulated from a proximal His bundle position (S) with an intracellular recording electrode in the penetrating portion of the His bundle (Hb) and extracellular bipolar electrodes from the proximal right (Rb) and left (Lb) bundles (marked by **arrows**). CL = cycle length; M = muscle potential.

potentials and augmentation of maximal upstroke velocity. The rate of recovery varied among preparations and within different portions of the His bundle and proximal bundle branches. However, during superfusion of up to 4 hours no preparation recovered to a state that might be described as normal, that is, similar to the state of nonischemic control preparations. Figure 6, panel B, shows resting and action potentials of a Purkinje cell from the branching portion of the His bundle in various states of recovery.

Conduction disorders and effect on action potentials in ischemic His-Purkinje system: An obvious correlate of the changes seen in the action potentials recorded from the ischemic proximal His-Purkinje system was the demonstration of slow conduction. An increase in the degree of conduction delay between the His bundle and proximal bundle branches together with intermittent failure of transmission could be demonstrated by increasing the driving rate. This is shown in Figure 7.

Figure 7, panel A, shows the arrangement of the stimulating and recording electrodes. Panel B shows a recording obtained 30 minutes after excision at a driving rate of 132/min. There is 1:1 conduction between the His bundle and proximal bundle branches. Recording of the transmembrane action potential from the His bundle shows diminished resting and action potentials with reduced upstroke velocity. These changes are reflected in the delayed inscription of the electrograms from the proximal right and left bundles (both are inscribed simultaneously) with an Hb-Lb conduction time of 45 msec. Panel C shows that increasing the driving rate resulted in Wenckebach periodicity. The action potential recorded from the His bundle is strikingly changed in both duration and configuration in relation to changes in the state of transmission. The opening action potential of the Wenckebach cycle (the first and seventh action potentials) has a normal-looking plateau. The second and subsequent action potentials have a hump-like inflection on the plateau. The inscription of the notch on the plateau coincides almost exactly with the bipolar electrograms recorded from the proximal right and left bundles. Starting from the third action potential the notch is gradually inscribed later on the plateau while the bundle branch electrograms are inscribed at an equal pace with a resultant increase in the transmission time between the His bundle and bundle branch recordings. Finally, impulse transmission fails and the bundle branch electrograms are not recorded. The action potential recorded from the His bundle that corresponds to a dropped beat (the sixth action potential) has no hump-like prolongation of the plateau and is significantly shortened.

Critical analysis of the Hb-Lb conduction times during the Wenckebach period in Figure 7, panel C, reveals an interesting arrangement. The Hb-Lb conduction time of the opening beat of the Wenckebach period is the shortest (45 msec). The second Hb-Lb interval is significantly prolonged to 76 msec. However, the third Hb-Lb conduction time is again shortened to 68 msec then gradually increases to 76 msec and 102 msec before the final failure of transmission. This variation of the typical Wenckebach periodicity represents the in vitro correlation to the in vivo observation shown in Figure 3, panel B. Analysis of the action potential duration of the first two beats of the Wenckebach cycle provides an explanation for this arrangement. The duration of the second action potential in the Wenckebach period measured at 50 percent of its peak amplitude is about 10 msec shorter than the opening action potential. The action potential duration then becomes gradually longer with the longest action potential being the one inscribed immediately before the dropped beat and associated with the longest Hb-Lb conduction delay.

Figure 7, panel D, was recorded 2 hours after excision.

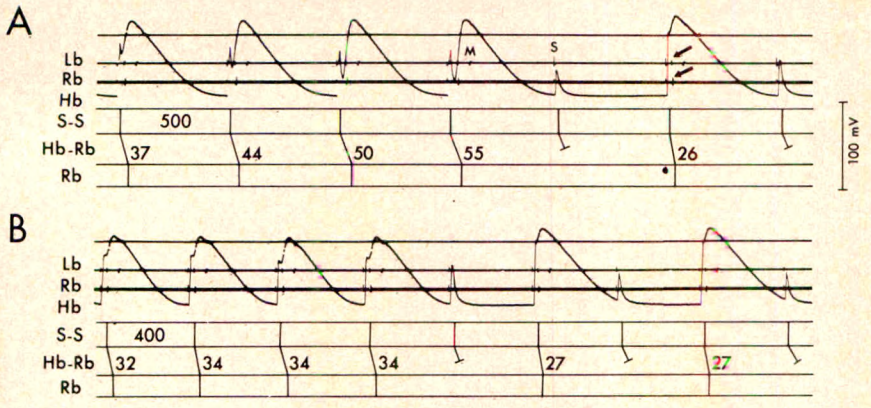

FIGURE 8. Recordings from the proximal His-Purkinje system in an ischemic preparation showing change from a Wenckebach type of conduction (record A) to a Mobitz type II block (record B) on recovery during superfusion. See text for details. The arrangement of the stimulating (S) and recording electrodes is the same as in Figure 7.

The preparation showed partial recovery during superfusion with an increase in the resting and action potentials and an increased upstroke velocity of the His bundle cell. These changes were also reflected in improvement of conduction between the His bundle and bundle branches with 1:1 transmission sustained up to a cycle length of 330 msec. At a shorter cycle length of 310 msec a regular repetition of the alternation between a 3:2 Wenckebach cycle and 2:1 block was seen. The alternation is explained by a slightly shorter action potential duration of the opening beat of the 3:2 Wenckebach cycle compared with that of the conducted beat during the 2:1 block. This observation represents the in vitro correlation of the frequent in vivo finding of 2:1 block after the blocked impulse in second degree A-V block (Fig. 2).

Recovery of conduction in His-Purkinje system: The process of recovery during superfusion with improvement of conduction frequently allowed the demonstration in the same preparation of two phenomena: (1) Early after the excision, pacing resulted in failure of transmission preceded by significant increment of conduction delay equivalent to the Wenckebach conduction; and (2) later in the experiment, failure of transmission could occur with only a few milliseconds' increment of conduction delay that simulated Mobitz type II block. This is shown in Figure 8.

In Figure 8, the arrangement of the stimulating and recording electrodes is the same as in Figure 7, panel A. The record in panel A was obtained 45 minutes after excision and shows the last part of a long Wenckebach cycle during pacing at a rate of 120/min. There was a gradual increase of the Hb-Rb conduction time from 26 msec (not shown in the figure) to 55 msec before failure of impulse transmission. The action potential recorded from the His bundle shows very characteristic alterations in relation to changes in the state of transmission. The first action potential in the record has a notch between the spike and plateau that gradually widens with the inscription of a double component action potential. The initial component (the spike) shows gradual loss of amplitude in spite of a constant rapid slope of the initial depolarization. The second component is a dome-shaped depolarization with an amplitude much greater than that of the initial spike, resulting in an overshoot whereas its maximal slope is considerably slower. The bipolar electrograms of the right and left bundles, which are more or less simultaneously inscribed, show a temporal relation to the second depolarization and are recorded correspondingly later, resulting in a gradual increase of the Hb-Rb and Hb-Lb conduction times. The action potential corresponding to the dropped beat shows disappearance of the second depolarization with the inscription of a low amplitude spike with a markedly shorter duration.

Panel B was recorded 90 minutes after excision. Pacing applied at a faster rate of 150/min resulted in intermittent failure of transmission. A constant Hb-Rb conduction time precedes the blocked beat, but after the block there is a 7 msec. shortening of the Hb-Rb conduction time together with a noticeable increase in the amplitude of the action potential recorded from the His bundle. Thus, in spite of the constant conduction time before the blocked beat, this arrangement actually represents a long Wenckebach periodicity with only a few milliseconds' increment of conduction delay.

Wenckebach periodicity: As in the in vivo study, typical Wenckebach periodicity was not common. Several variations of the Wenckebach phenomenon were seen. One of these variations is shown in Figure 7, panel C. Another variation is shown in Figure 9.

In Figure 9, the sketch at the lower right corner illustrates the arrangement of the stimulating and recording electrodes. The figure shows a 6:5 Wenckebach cycle. The action potential recorded from the His bundle has a characteristic configuration. There is a slow initial step followed by a more rapid but still abnormally slow upstroke. The His bundle electrogram (recorded within a 1 mm distance) reveals a very diminutive deflection that coincides with the beginning of the initial slow step. The electrogram recorded from the right bundle coincides almost exactly with the inscription of the rapid upstroke and is inscribed simultaneously with it during the Wenckebach cycle. In the last beat of the Wenckebach cycle the rapid upstroke fails and only a long slow step is inscribed. Correspondingly, conduction to the right bundle fails, as shown by absence of the right bundle electrogram.

The conduction time between the Hb and Rb electrograms during the Wenckebach cycle reveals an interesting arrangement. There is a clear alternation of Hb-Rb conduction time with an overall gradual increase in conduction delay. The alternation of Hb-Rb conduction time is explained by a peculiar relation between the time of takeoff of the rapid upstroke from the slow initial step and the duration of the ensuing action potential. Thus, the earlier the takeoff of the rapid upstroke, the longer the duration of the action potential. The long action potential duration results

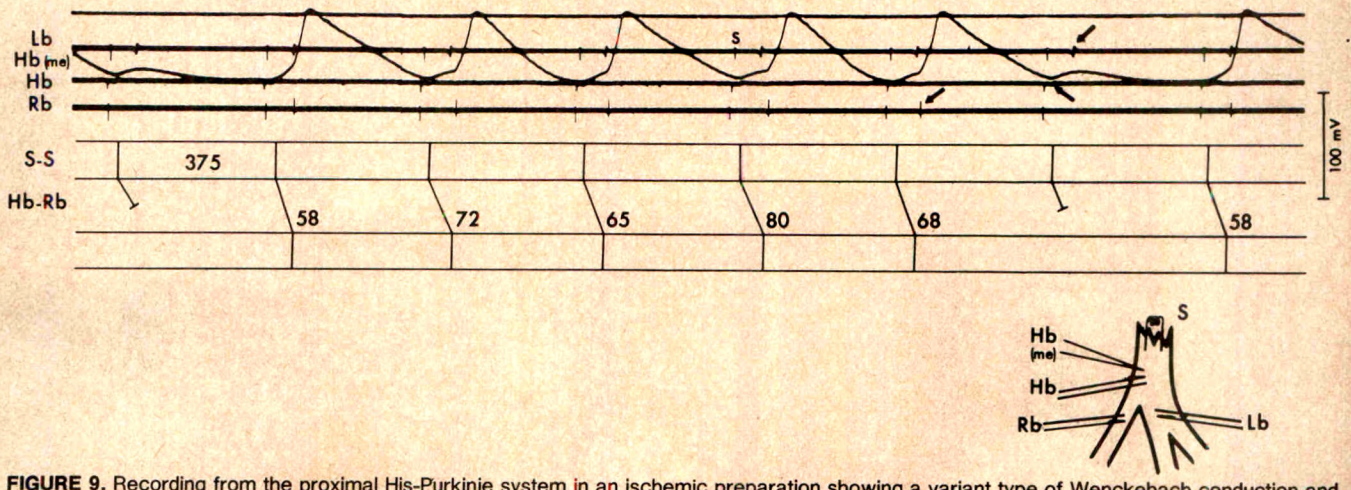

FIGURE 9. Recording from the proximal His-Purkinje system in an ischemic preparation showing a variant type of Wenckebach conduction and evidence of longitudinal dissociation in the ischemic His bundle. See text for details. The preparation was stimulated from the proximal His bundle (S), and both an intracellular microelectrode (Hb-me) and an extracellular bipolar electrode (Hb) were applied within a 1 mm distance to the penetrating portion of the His bundle. In addition, a bipolar electrogram was recorded from the proximal right and left bundles (Rb and Lb, respectively). The **arrows** point to the Hb, Rb and Lb electrograms.

in the inscription of the next foot potential before the completion of repolarization of the previous impulse. This leads to a delayed takeoff of the next rapid upstroke and a shorter action potential. This process regularly alternates with an overall increase of conduction delay until the last beat of the Wenckebach cycle when the fast potential starts from a relatively lower diastolic potential and fails to conduct.

The record in Figure 9 also shows that while this peculiar Wenckebach cycle is taking place between the sites of His bundle and right bundle branch recordings, there is a 1:1 response with delayed transmission at the left bundle branch recording. Thus, the right and left bundles are showing two different conduction patterns to stimulation from the proximal His bundle. The presence of a close temporal relation between the His bundle recording and conduction to the right bundle and the absence of such a relation between it and conduction to the left bundle strongly suggest that longitudinal dissociation and asynchronous conduction are taking place in the His bundle itself.

Tachycardia-dependent paroxysmal A-V block: In some of the experiments, the in vitro correlation of the in vivo observation of tachycardia-dependent paroxysmal A-V block (Fig. 5) could be demonstrated by a critical increase of the driving rate. This is shown in Figure 10.

In Figure 10, the arrangement of the stimulating and recording electrodes is the same as in Figure 7. Panel A shows 1:1 conduction between the His bundle and both bundle branches at a slow driving rate of 40/min. Panel B shows that increasing the driving rate to 75/min resulted in a 3:2 response. There is a slight increment of the Hb-Lb conduction time before the blocked beat. The His bundle recording shows only a local potential during failure of transmission. Panel C shows a further increase of the driving rate to 111/min, which resulted in complete failure of transmission. The His bundle recording shows repetitive local potentials with failure of inscription of a regenerative action potential. Both the intermittent failure of transmission in panel B and the complete failure in panel C occurred at driving cycle lengths that far exceeded the action potential duration so that stimuli applied quite late in diastole failed to conduct.

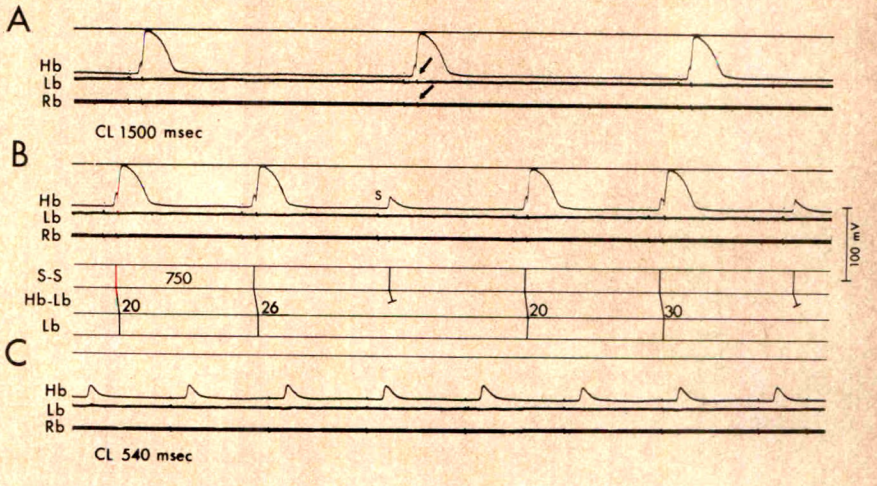

FIGURE 10. Recordings from the proximal His-Purkinje system in an ischemic preparation showing tachycardia-dependent paroxysmal block. The arrangement of the stimulating (S) and recording electrodes is the same as in Figure 7. See text for details.

Discussion

Correlation of In Vivo and In Vitro Observations on Second Degree A-V Block

The occurrence of similar phenomena in vivo and in vitro argues for the relevance of the data obtained in these studies. Exposure of the His bundle entailed more mechanical trauma than is usually employed in studies of the conduction system in vitro. However, comparison of the data obtained from control and infarcted preparations strongly suggests that the disturbances observed in the infarcted specimens were due to ischemia rather than to mechanical trauma.[13] In the present study several correlations between the in vivo and in vitro observations have been cited. By far the most significant correlative evidence concerns the presence and magnitude of increment of conduction delay in second degree A-V block in the proximal His-Purkinje system. Our in vivo observations have shown that an increment of conduction delay almost always precedes the blocked impulse. This increment may be as small as 1 or 2 msec at the early stages of second degree A-V block and may gradually increase up to 180 msec. Although an increment of 1 or 2 msec is within the measurement error in our in vivo study, it is possible that at a more rapid recording speed an increment of a fraction of a millisecond may have been detected. In vitro observations recorded at more rapid recording speeds have consistently shown some increment of conduction time prior to the blocked impulse. The process of recovery of conduction during superfusion allowed a unique opportunity to observe the correlate of the in vivo pattern of evolution of second degree A-V block in the reverse order. Thus, early after excision, one can observe a greater degree of increment of conduction delay during second degree block that on recovery during superfusion may gradually decrease to only a few milliseconds.

Both the in vivo and in vitro observations strongly suggest that Mobitz type II block and the Wenckebach type of conduction are not two distinct electrophysiologic processes but represent different degrees of the same process. Mobitz type II A-V block probably represents an early stage of departure from the normal His-Purkinje system conduction characteristics and is associated with a minimal increment of conduction delay that may not be detected at relatively slow recording speeds.

Action Potential Changes in the Ischemic His Bundle

The evidence obtained in this study shows characteristic changes in both the duration and configuration of action potentials in the ischemic His bundle depending on the state of transmission and the temporal relation of the impaled cell to areas of slow propagation and block. We have shown that greatly slowed propagation may lengthen the action potential and that failure of propagation may shorten it. At least two characteristic changes in action potential configuration were observed. The first pattern is a hump-like slurring of the plateau that can sometimes result in significant prolongation of the action potential. In the second pattern, the depolarization limb takes off from a very distinct step or foot potential and on failure of propagation only the step is recorded. Similar changes in action potential were described in the A-V node[19,20] and in Purkinje fibers superfused with high concentrations of potassium ion[21] and were ascribed to interaction between regions proximal and distal to areas of slow propagation. The hump-like inflections on the repolarization limb and the steps on the depolarization limb represent electrotonic spread to cells upstream and downstream, respectively, to areas of slow propagation.[20,21]

We have seen a third characteristic pattern of action potential configuration that we believe may represent recording in a region closely bordering the depressed area (Fig. 8). It is likely that the split action potential in Figure 8, panel A, could be explained on the basis of a single cell activity with dissociation between a rapid sodium ion current and a slow calcium ion current. However the gradual decrease in the amplitude of the initial spike without a change in the rapid slope of the initial depolarization may suggest an alternative explanation. Thus the spike may be attributed to electrotonic spread from a normal His bundle fiber characterized by a large spike, whereas the large dome-like second component may represent the activity of the cell impaled by the microelectrode that may be showing the slow response. Similar action potential configurations have been reported in human atrial strips and have been attributed to nonhomogeneous excitation of the preparation.[22] The very brief action potential recorded in Figure 8 during conduction block resembles the spike-like responses observed by Churney and Oshima.[23]

Nature of Slow Conduction in Ischemic His-Purkinje System

Slow conduction in cardiac muscle, best exemplified in the region of the A-V node, has been attributed to several factors including variations in geometry and changes in membrane properties or intercellular connections.[24] Recently, however, several lines of evidence have been reported to suggest that the cardiac action potential might be composed of a fast component and a slow component.[25–31] The fast component, which gives rise to the initial spike in normal cardiac muscle, is linked to the rapid sodium channel.[32] The slow component seems to be related to the slow inward channel which may be used by either sodium ion or calcium ion. It has been suggested that both the action potential and conduction characteristics of the A-V node might represent properties of the slow response.[33] The slow response has also been described in several experimental preparations including Purkinje strands exposed to increased potassium ion or increased potassium ion plus epinephrine.[28,31] An extensive review of the characteristics of the slow response has recently been published.[34]

This study has shown a remarkable similarity be-

tween action potential changes and characteristics of conduction in the ischemic His-Purkinje system and conduction in both the normal A-V node and Purkinje fibers subjected to a variety of pathophysiologic interventions. Most of our observations could be explained by suggesting that the ischemic His-Purkinje system shows the characteristics of the slow response. We have to account, however, for the observed evolution from second degree A-V block with no perceptible or minimal increment of conduction delay to one that shows a greater degree of increment; both are considered in this study to represent various degrees of the same electrophysiologic mechanism. Two factors may be implicated: The first suggests a greater degree of deterioration of the membrane responses of ischemic Purkinje cells; the second postulates a larger population of Purkinje cells with an abnormal response. Thus, second degree A-V block with a minimal increment of conduction delay may represent a lesser degree of derangement of the membrane responses or involvement of a relatively small but strategically positioned area of the His-Purkinje system, or both. Further studies including histopathologic correlations may define the role played by either factor.

On the other hand, this study may suggest that the characteristic low safety factor of conduction of the slow response,[34] which can result in single or repetitive failure of transmission, should not be temporally related to slow conduction. The latter is probably more linked to the size of the Purkinje population showing the slow response, and very slow conduction may be accounted for by summation of a series of slow or even discontinuous propagations.[21,35] Thus, the low safety factor of conduction may be operative in the early stages of second degree A-V block when there is a relatively lesser degree of slow conduction. Meanwhile, there is some evidence to indicate that with the development of a greater degree of increment of conduction delay, there is less chance for the occurrence of intermittent complete failure of transmission (paroxysmal A-V block).

The relation of acute ischemia to the characteristic changes of conduction in the proximal His-Purkinje system that follow ligation of the anterior septal artery is far from simple. In a recent study from this laboratory,[35] we discussed evidence suggesting that factors other than hypoxia alone might be instrumental in the production of acute ischemic disorders in the conduction system. The latter probably result from prolonged exposure to a pathologic environment in vivo that may alter the ionic currents that flow during the generation of the action potential. The leak of large amounts of potassium ion from the intracellular to the extracellular space,[37] the increased release of catecholamines[38] and other factors may be implicated. These factors are known to favor the occurrence of the slow response.[34] On the other hand, the recovery of Purkinje fibers in vitro can be ascribed to the washout of these deleterious factors.[36]

Refractoriness in the Ischemic His-Purkinje System and Tachycardia-Dependent Block

The electrophysiologic properties of normal and diseased Purkinje fibers are distinctly different. The refractory period in normal Purkinje fibers depends on a normal voltage-time course of the sodium pump and the end of repolarization usually signals full recovery of excitability.[32] On the other hand, the excitatory response of diseased Purkinje fibers depends on flow of current through channels whose time- and voltage-dependent conductance are different, and full recovery of excitability may extend late in diastole after completion of repolarization.[21,34] We have shown severe impairment of conduction, single and repetitive block, at cycle lengths that far exceed the action potential duration. However, a close relation still exists between the action potential duration and refractoriness in ischemic His-Purkinje cells. We have illustrated that the well known effect of rate and rhythm on the duration of the action potential can explain the common occurrence of 2:1 block after the dropped beat in second degree A-V block. It can also explain the Ashman phenomenon during the Wenckebach periodicity shown in Figures 3B and 7C. Similar conduction patterns were described in Purkinje fibers superfused with high levels of potassium ion and were explained on the same basis.[21] Thus, it seems that although refractoriness in ischemic Purkinje cells still maintains a proportional relation to the action potential, the duration of the two is not equal.

The concept of refractoriness that outlasts the action potential duration is of vital significance in understanding tachycardia-dependent block. Several authors[39,40] have attempted to interpret the situation in the pathologic His-Purkinje system by extrapolating from electrophysiologic data in normal His-Purkinje systems, in which impairment of conduction of a premature stimulus or during rapid rates can be ascribed to stimulation in phase 3. In a recent report by Rosenbaum et al.[39] an inordinate lengthening of the action potential has to be assumed to account for the so-called phase 3 block in some clinical records of tachycardia-dependent block. On the other hand, the clinical relevance of the recently popularized "gate" concept,[40] which was again based on studies of the normal His-Purkinje system, may be questioned. Thus, severe impairment of conduction in the ischemic His-Purkinje system can occur at cycle lengths that far exceed the longest action potential that could be recorded at any "gate" in the normal heart. This underscores the need for more electrophysiologic studies in the pathologic situation.

Unified Hypothesis for Second Degree A-V Block

According to current concepts,[41,42] the first type of second degree A-V block is considered to represent primarily A-V nodal block whereas the second type indicates block below the A-V node. However, recent clinical[43] and experimental observations[7,8,44,45] in addition to the findings in the present study show the

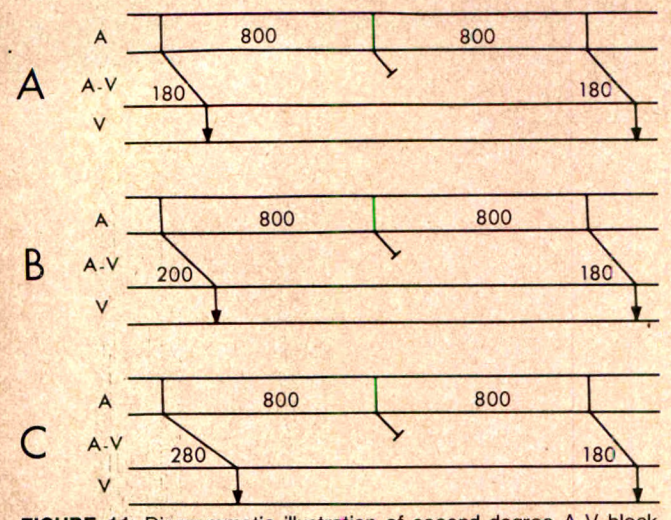

FIGURE 11. Diagrammatic illustration of second degree A-V block based on the suggested electrophysiologic mechanism. See text for details. The diagrams depict only the beat immediately preceding and the one immediately following the blocked impulse. A, A-V and V represent activation of the atria, A-V junction and ventricles, respectively. All values are in milliseconds.

common occurrence of Wenckebach conduction in the His-Purkinje system. Moreover, within the limitations of the available technique of His bundle recordings in man, it is possible that an intra-His bundle Mobitz type II (Fig. 5) or Wenckebach conduction (Fig. 3B) may be mistaken for A-V nodal Mobitz type II block or Wenckebach conduction.[7] In fact, in light of the long-standing misconception in the diagnosis of Mobitz type II block—which undoubtedly stemmed from limited insight into the underlying electrophysiologic mechanism—several records designated classic Mobitz type II may turn out to be examples of Wenckebach conduction. The diagnosis of Mobitz type II was originally based on the presence of constant P-R intervals before the dropped beat without emphasis on the necessity for a constant P-R in the beats immediately preceding and immediately following the block. Thus, several records of long Wenckebach cycles in which the last conducted beats before the blocked impulse showed no perceptible or a few milliseconds' increment of conduction delay were diagnosed as Mobitz type II block. Some of these records have recently been reported as examples of Mobitz type II in the A-V node,[46–48] and the blocked impulse occasionally coincided with slight shortening of the P-P interval.[46] A similar conduction pattern was shown to occur in the proximal His-Purkinje system in this study (Fig. 4).

Some authors[42] have expressed the idea that slight shortening of the P-R interval (not exceeding 20 msec) in the beat after the intermittence is acceptable in records otherwise characteristic of Mobitz type II block. It is clear, however, that a 20 msec difference in A-V conduction time between the beat immediately preceding and the one immediately following the block can occur only if there is an overall increment of conduction delay of 20 msec whether the increment is equally distributed in all beats of the Wenckebach period or inscribed in only one or two beats. Not only clinical records designated as Mobitz type II block actually represented Wenckebach conduction, but also some in vitro records previously published as examples of Mobitz type II block revealed the presence of a few milliseconds' increment of conduction delay.[49] A similar conclusion was emphasized in a recent study in which 98 percent of intracellular records of second degree block showed various degrees of increment of conduction delay when tracings were obtained at more rapid sweep speeds.[45]

Conduction in A-V node vs. His-Purkinje system: An understanding of the mechanisms of conduction in the A-V node can help to emphasize that second degree A-V block with no perceptible increment of conduction delay (the equivalent of Mobitz type II) is not expected to occur in the A-V node. All available reports indicate that conduction in the A-V node is normally slow. As mentioned, several authors entertain the possibility that normal A-V nodal cells show characteristics of the slow response. Thus, the A-V conduction system can be viewed as consisting of a proximal portion normally showing the characteristics of the slow response (the A-V node) and a distal portion normally showing the properties of the fast response (the His-Purkinje system). Under the influence of a variety of pathophysiologic interventions—exemplified in this study by acute myocardial ischemia—the His-Purkinje system gradually loses the characteristics of the fast response and begins to show properties of the slow response. At an early stage of departure from normal, the His-Purkinje system may show second degree A-V block with no perceptible to a few milliseconds' increment of conduction delay. On further departure from normal, the His-Purkinje system resembles the A-V node in showing a significant increment of conduction delay before the blocked impulse. To reiterate, the A-V node, since it cannot normally show the fast response of normal His-Purkinje system, is not expected to illustrate the earlier stages of departure from the fast response.

Classification of second degree A-V block: On the basis of this study, coupled with current understanding of the electrophysiology of A-V nodal conduction, it is suggested that second degree A-V block should be classified according to the degree of increment of conduction time as calculated in the beat immediately preceding and the one immediately following the blocked impulse (Fig. 11). The classification does not primarily consider the behavior of the P-R interval preceding the blocked impulse nor the duration of the QRS complexes in the conventional leads.[50] According to this classification, second degree A-V block can occur with no perceptible increment of conduction delay or can show an increment of 1 up to several hundred milliseconds. When second degree A-V block occurs with no perceptible increment of conduction delay (Fig. 11A), the lesion is

probably localized in the His-Purkinje system. In accordance with the hypothesis presented in this study, it also seems logical to assume that when second degree A-V block occurs with only a few milliseconds' increment of conduction delay (Fig. 11B), the disorder is probably localized in the His-Purkinje system rather than in the A-V node, which usually shows more significant increments of conduction delay. Second degree A-V block with significant increments of conduction delay (Fig. 11 C) could be localized in either the A-V node or His-Purkinje system. This classification has one obvious limitation in the occasional case in which the shortened P-R interval after the block is caused by a fortuitous A-V junctional escape beat and does not reflect the genuine A-V conduction time. However, this does not weaken the general concept since it holds only for the few exceptional cases in which no perceptible increment of conduction delay precedes the block. The recording of a long rhythm strip and spontaneous or induced change in the atrial rate may help to unravel these cases.

Clinical implications: This study has presented sufficient evidence to justify abandoning the term Mobitz type II block, at least when describing electrophysiologic mechanisms. The term does not represent an electrophysiologic entity but probably an imaginary line of departure from the characteristics of the fast response to those of the slow response. There also seems to be little advantage in the term Wenckebach type of conduction. Originally the term was used to refer to a characteristic arrangement in which a gradual beat to beat increment of conduction delay precedes the blocked impulse. That this is not necessarily the case is shown in the present study and others.[1,49] Our study seems to indicate that the overall increment of conduction delay is more important than the behavior of the P-R intervals before the blocked impulse. The empirical classification of second degree A-V block into types I and II is still very useful clinically because the relatively small increment often seen with infranodal lesions cannot be measured on the conventional electrocardiogram. However, this study is primarily a plea to discard the old classification of second degree A-V block, and in particular the term Mobitz type II block, when describing electrophysiologic phenomena. On the other hand, this classification may still be applicable in clinical practice and in routine clinical electrocardiograms.

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Loud First Heart Sound with Long P-R Intervals

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A case of partial atrioventricular block with Wenckebach periods and a loud first heart sound (S_1) associated with the longest P-R interval of the cardiac cycles is described. Although the surface electrocardiogram provided no clues to this paradoxical behavior, the intraatrial electrogram revealed that the long P-R interval with the loud S_1 was accompanied by atrial echoes (reciprocal atrial beats). The loud S_1 with a very long P-R interval was always caused by an atrial contraction synchronous with the QRS complex.

Decreased intensity of the first heart sound in a cardiac cycle with a long P-R interval has been variously ascribed to (1) decreased rate of rise of left ventricular pressure, (2) earlier closure of the mitral valve, and (3) decreased rate of excursion of the atrioventricular (A-V) valves.[1–4] The first heart sound (S_1) during Wenckebach periods of partial A-V block should thus decrease in intensity with lengthening of the P-R interval, the longest P-R interval resulting in the softest S_1. This communication describes a patient whose S_1 gradually decreased in intensity with lengthening of the P-R interval until the last beat of the cycle (with the longest P-R interval) when it was louder than that of the opening beat. This paradoxical behavior could be explained by analysis of the simultaneous intracardiac electrocardiogram, which showed that the last beat of the cycle with the longest P-R interval had two P waves. The echo P wave was within the QRS complex and was thus not seen in the surface electrocardiogram. We postulate that atrial echo (reciprocal) beats were responsible for the loud S_1 associated with the long P-R interval.

Case Report

A 14 year old schoolboy was seen because of occasional dizzy spells. His family, personal and past history was noncontributory. Physical examination revealed a well developed, well nourished boy with a blood pressure of 110/70 mm Hg (supine) and 115/75 mm Hg (standing). Pulse rate ranged from 40 to 60/min and was irregular. The peripheral pulses were normal. The heart size was grossly normal. The first heart sound was irregular in rhythm and intensity, but the second sound was normal. No additional sounds were heard.

The electrocardiogram revealed a normal sinus rhythm and a P-R interval of 175 to 400 msec, a QRS interval of 60 msec and a QRS axis of +60°. A rhythm strip disclosed periods of sinus arrhythmia and atypical Wenckebach phenomena; that is, in the presence of marked sinus arrhythmia, there was progressive lengthening of the P-R interval, culminating in a pause without an obvious blocked P wave. The length of the P-R interval after the pause was reduced to that of the shortest in the cycles. The resting heart rate ranged between 30 and 50/min. With exercise, the sinus rate rose only to 70/min, and periods of Wenckebach continued. Hemogram and blood chemistry values were within normal limits. Urinalysis was unremarkable. Chest X-ray films revealed a normal-sized heart and clear lungs.

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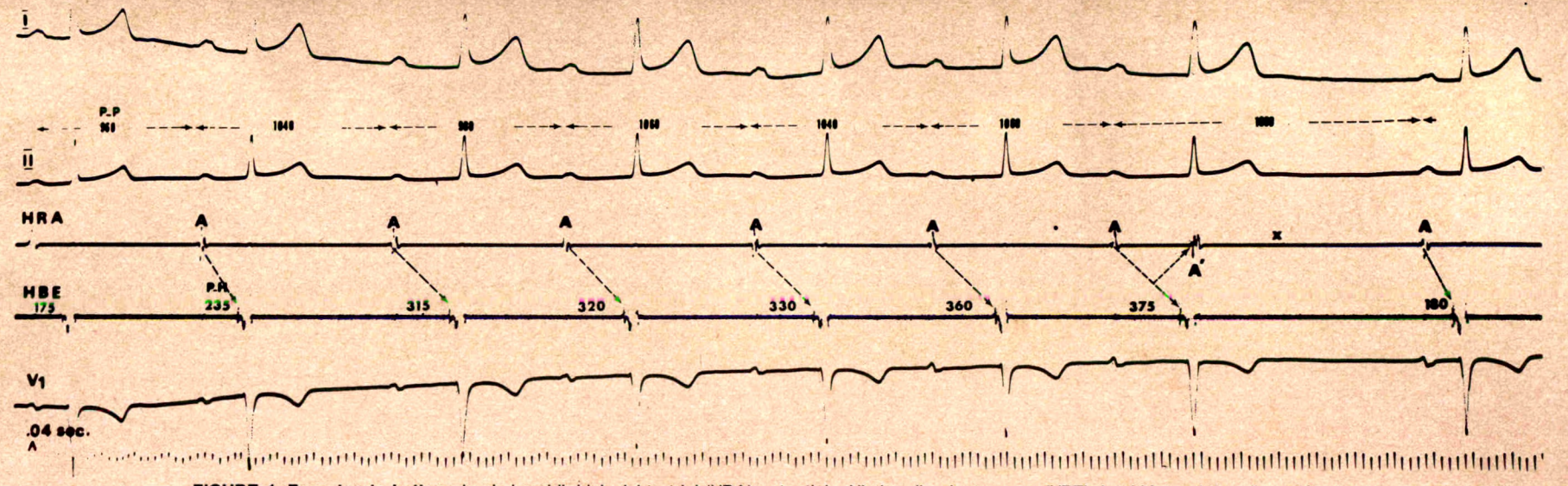

FIGURE 1. From top to bottom, leads I and II, high right atrial (HRA) potentials, His bundle electrogram (HBE), lead V_1, and time lines 40 msec apart. (See text.)

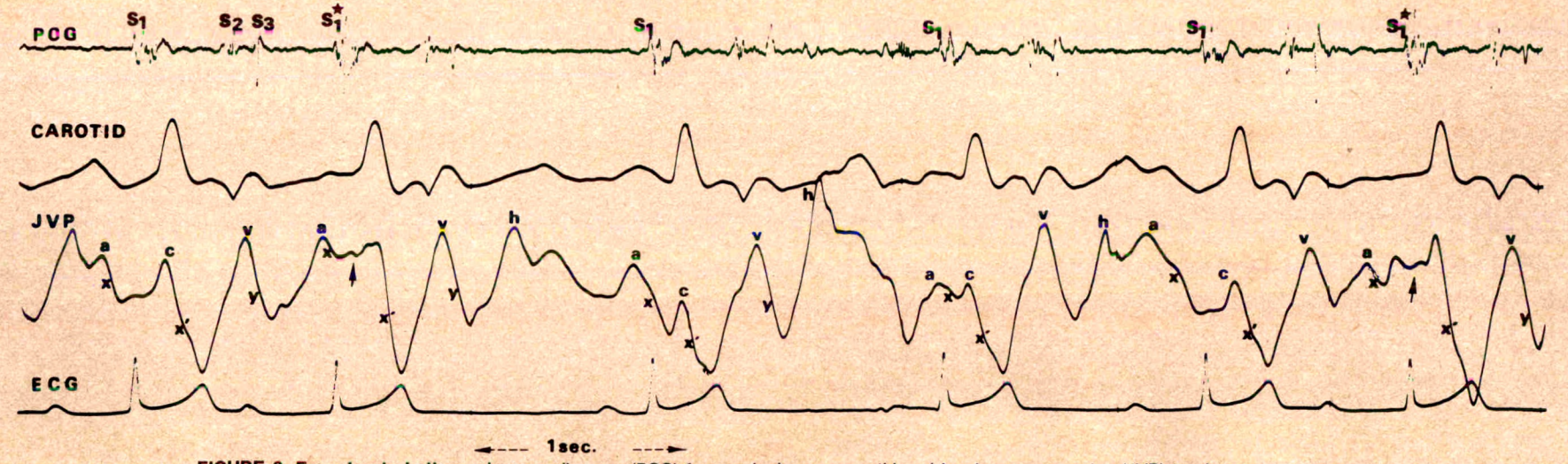

FIGURE 2. From top to bottom, phonocardiogram (PCG) from apical area, carotid and jugular venous pulse (JVP) tracings and electrocardiogram (ECG). (See text.)

Right Atrial and His Bundle Electrograms

Sinus and atrioventricular nodal function was studied by simultaneous recordings of leads I, II and V_1 and high right atrial and His bundle electrograms. At the same time, a surface phonocardiogram (from the apical area), carotid arterial and jugular venous pulse tracings and an electrocardiogram were recorded so that the arrhythmia could be correlated with the heart sounds and arterial and venous pulses.

Figure 1: The tracing shows marked sinus arrhythmia (sinus P-P intervals ranging from 960 to 1060 msec). From P_4 to P_7, sinus arrhythmia is mild. The first and the last P-R intervals are the shortest intervals; from 175 msec (P_1), the interval lengthens to 375 msec (P_7). This period of gradual prolongation of the P-R interval is terminated by an atrial echo (reciprocal) beat that resets the sinus node and the next P-R interval is reduced to 180 msec. This phenomenon was repeatedly observed even though the last P-R intervals of the Wenckebach periods ranged from 375 to 435 msec.

Figure 2: This tracing shows surface phonocardiogram, carotid and jugular venous pulse tracings and electrocardiogram. The first 2 beats represent the last 2 beats of a Wenckebach period. The sequence from P_3 to P_6 is a complete Wenckebach cycle, revealing progressive lengthening of the P-R interval. P_3 is the control beat with the shortest P-R interval. The S_1 of this beat is the loudest (from beat 3 to beat 5) and becomes gradually softer with an increasing P-R interval, until the longest interval of the cycle is reached, when S_1 becomes even louder than in the opening beat of the cycle (beats 6 and 2). In the jugular venous pulse tracing beats 1, 3 and 5 have normal *a*, *c*, *x*, *v* and *y* waves. The *a* wave of the 4th beat is different because P_4 is not a sinus P wave. Beats 2 and 6 are similar; the *x* wave is abbreviated and interrupted by a positive wave between the *a* and *c* waves. This positive extra wave can be caused only by a premature atrial systole. Since the atrial electrogram showed that the Wenckebach periods were terminated by atrial echoes, it is reasonable to assume a similar occurrence during the P-R interval of beats 2 and 6. It is during these P-R intervals that S_1 is even louder than during the P-R intervals of the opening beats of the cycles. It may thus be surmised that the atrial echoes associated with the long P-R intervals are responsible for the increased intensity of S_1. That these echoes are the sole factor in accentuating S_1 can be seen by comparing the P-R intervals of beats 1 and 6. These intervals are 370 and 380 msec, respectively, but S_1 is loud only during beat 6, which is associated with an atrial echo. That a long P-R interval alone does not produce a loud S_1 can be seen by comparing beats 1 and 2. The P-R interval of beat 1 is 370 msec, but S_1 is not loud. With slightly greater prolongation of the P-R interval to 410 msec an atrial echo is produced resulting in a loud S_1.

Discussion

The inverse relation between the length of the P-R interval and the intensity of S_1 has been shown to be dependent upon the relation between atrial and ventricular systole. That this relation does not always hold true was noted (without adequate explanation) by Wolferth and Margolies,[5] who showed in two of their patients (Cases 4 and 5), that S_1 became louder as the P-R interval lengthened to 0.34 and 0.32 second, respectively. Levine and Harvey[6] also stated: "... first sound may be normal, especially if the P-R interval is greatly prolonged ... some of the faintest first sounds occur with the slightest degree of A-V block (0.21 to 0.24 seconds) ... however, we have sometimes heard normal first sound intensities with more prolongation (0.26 to 0.30 seconds), and then with greater delay (0.34 seconds) found that the first sound decreased." They noted that during Wenckebach periods "some ranges of P-R prolongations are associated with normal rather than faint sounds."

It is also known that atrial systole and relaxation can open and close the A-V valves.[2,7,8] Thus, with a long P-R interval, A-V valve closure will occur well before ventricular systole. Shah et al.[2] showed that such closure is a silent event and the intensity of S_1, under such circumstances, is totally dependent upon left ventricular systole. As the P-R interval gets shorter, A-V valve closure begins to coincide with ventricular systole, S_1 becomes louder and its amplitude becomes directly proportional to the rate of mitral valve closure. Theoretically, the loudest S_1 in a given patient would occur when A-V valve closure occurs at a time of maximal rate of rise of left ventricular pressure. In other words, a loud S_1 could result if the A-V valves are still open at the time of maximal rate of rise of left ventricular pressure, as is generally taken to be the case with the loud S_1 in mitral stenosis, conditions with increased flow, hyperthyroidism, short P-R interval and tachycardia. It is reasonable to propose therefore that, even in the presence of a very long P-R interval and closed A-V valves, the occurrence of another atrial systole could open the A-V valves during the maximal rate of rise of left ventricular pressure; the A-V valve motion would be decelerated and closed at a much faster rate, and a loud S_1 would ensue. A simple downward movement of the A-V valves (at the end of a long P-R interval) due to overdistension of the atria secondary to prolonged atrial filling would not cause a loud S_1 because (1) the A-V valves can be opened only by an active atrial contraction, and (2) the A-V valves cannot be pushed as far down in the ventricular cavity by passive gentle downward movement as by an active act of atrial contraction. It is thus understandable that a long P-R interval could be associated with a loud S_1 if that P-R interval causes longitudinal dissociation of A-V nodal conduction, causing an atrial echo and resulting in atrial contraction, which then coincides with the maximal rate of rise of left ventricular pressure. A loud S_1 would not result if the atrial echo or a premature atrial beat occurred after the maximal left ventricular pressure had been achieved.

This case supports this thesis clearly. We have shown that only a long P-R interval, associated with an atrial echo (Fig. 1), causes a loud S_1 (compare beats 1 and 6 in Fig. 2). This phenomenon may not be well known because when the atrial echoes fall within the QRS complex, the surface electrocardiogram fails to reveal them; it requires an intraatrial electrogram to demonstrate the phenomenon clearly. Beats 2 and 6 in Figure 2 show that atrial echoes (hidden in the QRS complex) resulted in an atrial contraction that was sufficiently forceful to cause an extra positive wave between the *a* and *c* waves of the jugular venous pulse tracing.

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Traumatic Right Coronary Arterial-Right Atrial Fistula

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A healthy 25 year old man presented with a machinery murmur and a history of a penetrating thoracic injury. Hemodynamic and angiographic evaluation demonstrated a fistula from the right coronary artery to the right atrium that was later successfully repaired. This case and similar reported cases indicate that fistula formation is a late complication of penetrating thoracic injuries. The onset of the murmur occurs with enlargement of the fistula and typically is delayed for several weeks to months after the initial injury.

Penetrating thoracic injuries rarely involve the coronary arteries but when present, laceration of the coronary artery usually leads rapidly to pericardial hemorrhage, tamponade and death.[1,2] Under certain circumstances, however, when injury to the coronary arteries is less severe, a penetrating cardiac injury may occur without an immediate change in hemodynamic status. In these cases the patient may present at a later date with a coronary arterial fistula as a complication of the original injury. The development of such a fistula during a 3 year interval after a penetrating thoracic injury prompted us to record this case.

Case Report

The patient, a 25 year old white airman, sustained multiple shrapnel wounds to the body in the Philippines; he arrived at the hospital 20 minutes later with acute respiratory distress and cyanotic appearance. A right thoracentesis relieved a tension hemopneumothorax and resulted in clinical improvement. Aspiration of the right chest cavity was continued for 5 days. The possibility of intraabdominal injury was excluded by an exploratory laparotomy. A chest roentgenogram taken on the 13th hospital day revealed marked straightening of the left border of the cardiac silhouette and obliteration of the left cardiophrenic sulcus that were interpreted as indications of pericardial and pleural fluid. The patient's condition improved, becoming clinically stable, and he was discharged from the hospital. Subsequent chest roentgenograms remained unchanged. A heart murmur was not noted during this hospitalization. Review of pertinent electrocardiograms was not possible because the records were destroyed by fire.

A heart murmur was noted during a reenlistment physical examination 3 years after injury. There was no prior history of a heart murmur although the patient had frequent medical examinations as a child, an adolescent and at the time of his injury. Cardiac auscultation was not performed during the 3 year interval after the injury. The patient was asymptomatic and no other relevant historical data were obtained.

On examination, the patient appeared normal. The blood pressure was 120/78 mm Hg and the pulse 76 beats/min. A shrapnel scar was present in the fifth intercostal space at the right sternal border. Palpation of the precordium revealed a right sternal impulse. A grade 4/6 continuous murmur was loudest along the lower right sternal border and radiated throughout the chest and to the neck. A chest roentgenogram (Fig. 1) revealed a globular cardiac silhouette suggesting right-sided enlargement. The pulmonary vascula-

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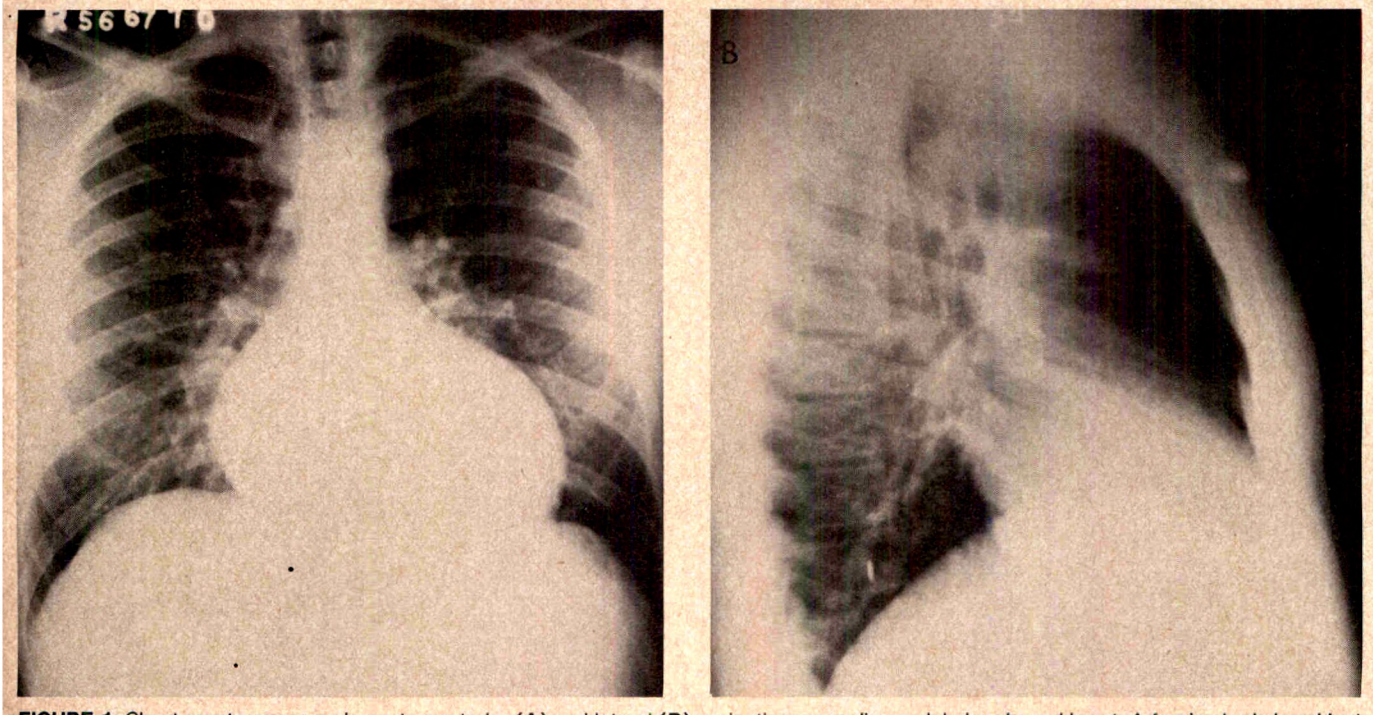

FIGURE 1. Chest roentgenograms in posteroanterior **(A)** and lateral **(B)** projections revealing a globular-shaped heart. A foreign body is evident in the left lower lung field.

ture appeared normal. A metallic fragment was noted behind the heart in the left posterior lung field. The electrocardiogram and vectorcardiogram (Fig. 2) revealed loss of inferior wall forces, suggesting an inferior myocardial infarction.

At cardiac catheterization, the mean pulmonary arterial and right atrial pressures were 12 and 3 mm Hg, respectively. An oximetry series demonstrated a left to right shunt at the right atrial level, which was confirmed by indicator-dilution curves. The magnitude of the shunt was calculated to be 22 percent of the rate of systemic blood flow, which was 5.1 liters/min.[3] The pulmonary arteriogram revealed a metallic fragment in the plane of a left lower lobe segmental pulmonary artery. A retrograde aortogram (Fig. 3) and a selective right coronary arteriogram revealed a right coronary artery of large diameter ending abruptly in a fistulous tract that emptied into the right atrium. Pulsatile flow in the right coronary artery distal to the fistula was present. Localized hypokinesis of the inferior wall at the base of the left ventricle was demonstrated in the left ventriculogram. Selective left coronary arteriography revealed extensive collateral blood flow to the right posterior descending coronary artery and fistula through prominent septal branches of the left anterior descending coronary artery.

At thoracotomy through a midsternal incision the pericardial space was found to be obliterated by fine fibrous adhesions. The pulsatile proximal right coronary artery was 1 cm in diameter and led to a fistulous tract approximately 6 cm from the aorta. An impulse was palpable over the fistula, which was formed by a single tract communicating with the right atrium in the atrioventricular groove. The right coronary artery distal to the fistula appeared normal. A mean blood flow rate of 782 ml/min was measured by an electromagnetic flowmeter positioned around the proximal right coronary artery. Mean blood flow decreased to 230 ml/min after occlusion of the fistula. The electrocardiogram remained stable during division and oversewing of the fistula. The postoperative course was uncomplicated and no cardiac murmur was detected.

Six weeks after operation the murmur remained absent and the electrocardiogram unchanged. No shunt was detected by an oximetry series or by indicator-dilution curves with central injection and sampling. The mean pulmonary arterial and right atrial pressures were 9 and 0 mm Hg, respectively. Localized hypokinesis of the left ventricle was unchanged from the previous study as visualized during left ventriculography. Selective coronary arteriography revealed diminution of the septal collateral blood flow, and the posterior descending coronary artery was supplied by antegrade flow from the right coronary artery. The lumen of the dilated right coronary artery was narrowed and irregular, suggesting partial obliteration by thrombus. The fistula was closed. Antegrade flow to the posterior descending artery and its branches appeared normal. During a Bruce multistage exercise capacity test, the patient stopped at stage V because of leg fatigue after achieving a heart rate of 180 beats/min.

Discussion

The site of injury in the right anterior chest wall and the position of the metallic fragment observed in the chest roentgenogram indicate that the probable course of the fragment was through the right anterior chest wall into the right atrium at the right atrioventricular groove and then by way of the pulmonary bloodstream to the left lower lobe pulmonary artery. The right coronary artery and adjacent myocardial wall were probably involved at that time. The fistula could have been formed in at least one of these two ways: (1) a traumatic aneurysm of the right coronary artery formed at the time of injury could have pro-

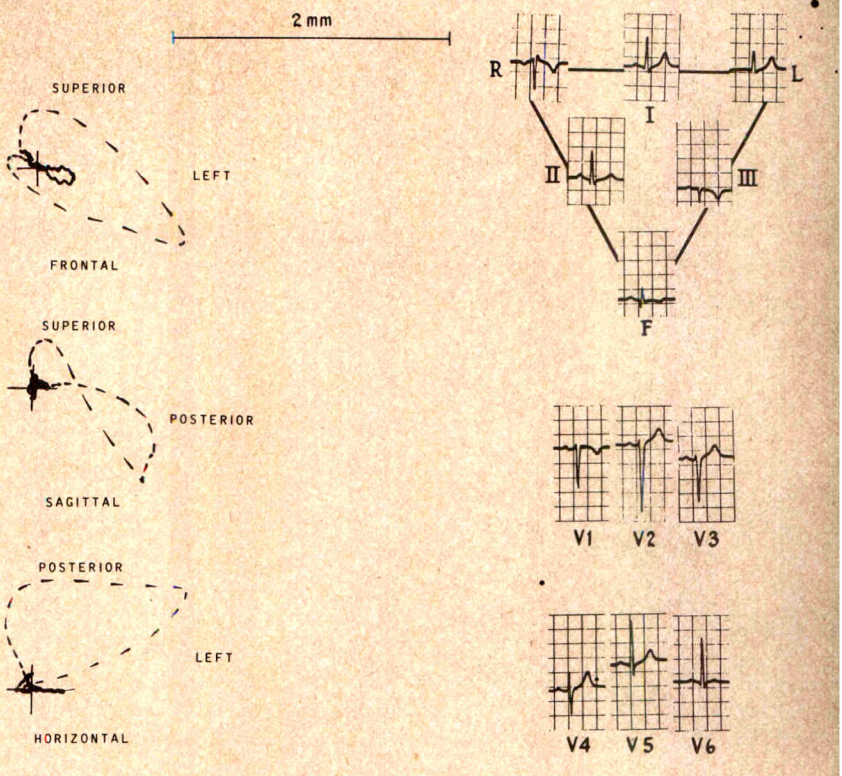

FIGURE 2. Scalar electrocardiogram **(right)** and vectorcardiogram **(left).**

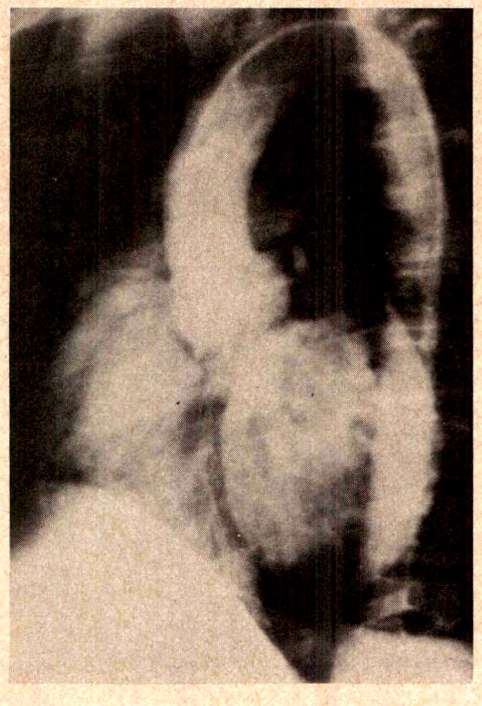

FIGURE 3. Aortogram in left anterior oblique projection **(left).** Artist's sketch **(right)** demonstrates the ascending aorta (Ao), dilated right coronary artery (RCA), fistulous tract and right atrium (RA). Contrast medium is visualized in the left ventricle (LV) because the catheter tip inadvertently entered the left ventricle during injection.

gressively enlarged and later ruptured into the right atrium[4,5]; or (2) a small coronary arterial fistula could have developed at the time of the injury and become progressively enlarged during the reparative process. The pericardial fluid noted on the 13th day after injury and the evidence of old myocardial infarction support the contention that the right coronary artery and right atrium were involved at the time of injury.[1]

Clinical features in reported cases: An interval between injury and the appearance of a continuous murmur is a prominent feature in cases of traumatic coronary arterial fistula (Table I). The interval ranged from several weeks to several months in 9 of the 10 cases of this lesion described in detail in the English language literature.[2,4,6–13] In the absence of a murmur, cardiac involvement may not be suspected

TABLE I

Ten Reported Cases of Traumatic Coronary Arterial Fistula*

Case no. and Reference	Evidence of Infarction on ECG	Months from Injury to Detection of Murmur	Site of Fistula	Duration of Follow-up (yr)	Fistula Repaired	Postoperative Persistence or Recurrence of Fistula
1[2,6]	ST-T	1/2	RCA to RA	20	No	...
2[4]	CRBBB	24	RCA to RA	9	Yes	No
3[7]	Inf	2	RCA to RA	13	Yes†	Yes‡
4[8]	Inf	0	RCA to RA and RV	1	Yes†	No
5[9]	ST-T	1/2	RCA to RCV	2 2/3	Yes†	Yes‡
6[10]	ST-T	1/2	RCA to RA	5/6	Yes	No
7[11]	Ant-lat	2	LAD to LV	4	Yes	No
8[12]	N	2	LAD to RV	1/2	No	...
9[13]	Inf	1/10	RCA to RA	1/4	Yes	No
10 (current case)	Inf	36	RCA to RA	4 1/2	Yes	No

* Two additional reported cases without clinical information[7,8] are excluded.

† Fistula recurred and was again repaired.

‡ Recurrence of fistula after initial repair without recurrence after second repair.

Ant-lat = anterolateral myocardial infarction; CRBBB = complete right bundle branch block; ECG = electrocardiogram; Inf = inferior myocardial infarction; LA = left atrium; LAD = left anterior descending coronary artery; LV = left ventricle; N = normal; RA = right atrium; RCA = right coronary artery; RCV = right coronary vein; RV = right ventricle; ST-T = nonspecific ST-T wave changes.

at the time of injury. However, the electrocardiogram is usually abnormal, commonly revealing a pattern of infarction in patients who later have a coronary arterial fistula.[7,8,11] This finding underlines the importance of recording an electrocardiogram in all patients with traumatic thoracic injuries. Surgical repair of the cardiac lacerations was performed at the time of injury in 3 of the 10 patients later discovered to have a coronary arterial fistula.[8,11,13] The fistula was not recognized at operation in any of these three patients. Four of the remaining seven patients had aspiration of a right hemothorax at the time of injury, and a right coronary arterial fistula eventually developed in all.[2,4,6,9] In the remaining three patients, cardiothoracic injury was unsuspected at the time of trauma.[7,10,12]

During the interval between the injury and discovery of the murmur and fistula the hemodynamic shunt apparently increases in size. This hypothesis is supported by the observation that the murmur may increase in intensity while the patient is being followed up,[8] and by the very large coronary arteries proximal to the shunt in our case and others.[4,8,10] It seems reasonable to assume that it would take time for these large proximal coronary arteries to dilate to this size. The major determinants of the size of the shunt are the compliance of the recipient cardiac chamber and the cross-sectional area of the fistulous tract.[14,15] Proximal dilatation of the coronary artery is a result of the hemodynamic alterations associated with the fistula, the most prominent changes being the increase in flow and change in pulse pressure along the length of the coronary artery.[16] In systemic arteriovenous fistulas, degeneration of the proximal artery has been noted; this may also pertain to the coronary arteries.[17] Once an equilibrium is established the size of the shunt and vessel may then remain stable for long periods.[6,14]

Surgical treatment: Indications for surgical intervention in patients with a traumatic coronary arterial shunt include prevention of infectious endarteritis or endocarditis and correction of the "coronary artery steal syndrome."[18] Endocarditis and endarteritis have been documented in patients with congenital coronary arterial fistula and, although they have not been described in patients with traumatic coronary arterial fistula, there is no reason to believe they could not occur in appropriate circumstances.[19–21]

Diversion of blood through the fistula, rather than occlusion of the coronary artery, may have resulted in insufficient blood flow through the right coronary artery and an inferior myocardial infarction in our patient. At the initial angiographic study, diversion of blood from the left anterior descending coronary artery to the posterior descending coronary artery and into the fistula was demonstrated to be by way of septal collateral vessels. This coronary arterial steal may have augmented the inferior wall hypokinesis revealed by left ventriculography. Although collateral vascular channels to the posterior descending coronary artery were probably still present, they were not visualized in the postoperative coronary arteriogram because the change in hemodynamics was such that they were not being utilized. This finding indicates the labile nature of these small intercoronary communications, which may appear or disappear rapidly as the hemodynamic load dictates.[13]

Complications of "coronary steal" in coronary arte-

rial fistulas may include angina pectoris, congestive heart failure and infarction.[4,6,7,11] Angina, ventricular failure and hypokinesis could conceivably be relieved by surgical intervention. However, in our case the hypokinetic inferior wall remained unchanged after closure of the fistula. Traumatic or acquired fistulas usually have fewer communications with the recipient chamber than do congenital fistulas, and the surgical result is therefore frequently more satisfactory.[17]

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Echocardiographic Findings in Right Coronary Arterial-Right Ventricular Fistula

Report of a Neonate with Fatal Congestive Heart Failure

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Coronary arteriovenous fistula is a rare cause of congestive heart failure in the newborn. We describe a 2 day old infant with a large fistula between the right coronary artery and right ventricle that caused fatal congestive heart failure. An echocardiographic study revealed a large right ventricle, paradoxical motion of the interventricular septum and an enlarged aorta, suggesting an unusual location of a left to right shunt. The diagnosis was established at cardiac catheterization when a large left to right shunt was found at the ventricular level; the fistula was visualized by angiography.

A fistula between a coronary artery and a right cardiac cavity seldom causes heart failure during infancy. This report describes a neonate with fatal congestive heart failure secondary to such a fistula, and reports and interprets the echocardiographic findings in relation to hemodynamic, angiographic and pathologic data.

Case Report

A 2 day old female infant was the product of an uncomplicated pregnancy and delivery. Twenty hours after birth her respirations were labored and she became cyanotic. A heart murmur and hepatomegaly were noted. Digoxin and furosemide were administered parenterally and she was transferred to the University of Iowa Hospitals.

Physical examination revealed a well developed infant with marked respiratory distress and moderate cyanosis. The weight was 2,440 g. Blood pressure, obtained by the Doppler method, was 70/38 mm Hg in the arms and 78/42 mm Hg in the legs. Heart rate was 150/min and respiratory rate 60/min. A systolic impulse was felt at the left lower sternal border. The heart rhythm was regular with a normal first sound and a single second sound. A diastolic gallop was heard at the apex. A grade 4/6 harsh pansystolic murmur was heard at the left and right sternal borders and a grade 2/6 mid-diastolic rumble at the left lower sternal border. The lungs had diffuse rales bilaterally. The liver edge was 6 cm below the right costal margin.

Chest roentgenogram revealed marked cardiomegaly, increased pulmonary vascularity and a collapsed right middle lobe. The electrocardiogram was normal. The infant was immediately given oxygen and her color improved. Arterial blood gas determinations during breathing of 100 percent oxygen revealed the following values: pH 6.99; partial pressure of carbon dioxide 23 mm Hg; partial pressure of oxygen 92 mm Hg and oxygen saturation 90 percent. Her condition improved after treatment with parenterally administered sodium bicarbonate, furosemide and digoxin and maintenance in an atmosphere of 40 percent oxygen.

An echocardiogram (Fig. 1) revealed two ventricles. The anterior ventricle was dilated (16.8 mm; normal 10.4 to 14.6 mm) and the posterior ventricle was normal (16.1 mm; normal 16.1 to 21.7 mm). The interventricular septum

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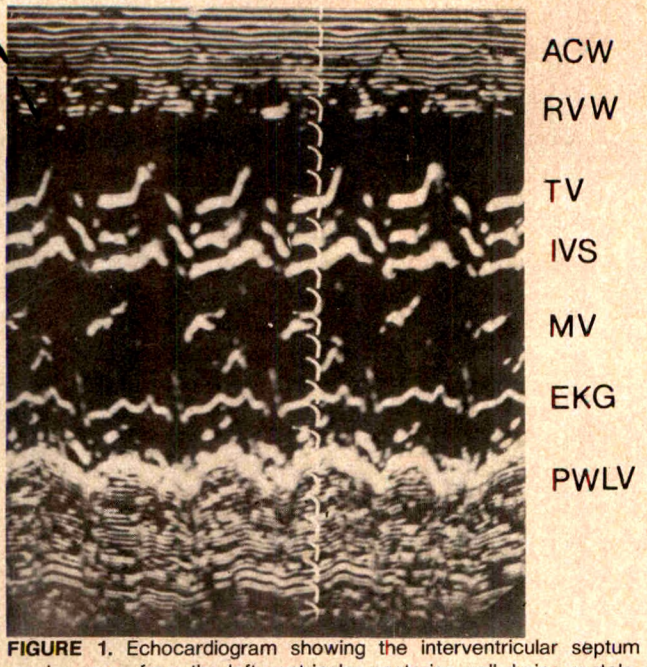

FIGURE 1. Echocardiogram showing the interventricular septum moving away from the left ventricular posterior wall during systole, indicating right ventricular volume overload (type A abnormal septal motion). ACW = anterior chest wall; EKG = electrocardiogram; IVS = interventricular septum; MV = mitral valve; PWLV = posterior wall of left ventricle; RVW = right ventricular wall; TV = tricuspid valve.

had an abnormal type A motion throughout the echo sweep from the mid-left ventricle to the mitral valve level, suggesting volume overload of the right ventricle.[1] The aortic root was dilated (14 mm; normal 9.3 to 11.3 mm). Measurement technique and normal values were described by Solinger et al.[2]

Cardiac catheterization: Despite decongestive measures the patient's condition deteriorated and emergency cardiac catheterization was performed (Table I). There were high levels of oxygen saturation in the superior vena cava and right atrium and a large left to right shunt at the ventricular level. The pulmonary-systemic flow ratio was 3.3. A small right to left shunt across a patent ductus arteriosus was present. The pulmonary arterial and right ventricular pressures were at systemic levels. End-diastolic pressures in both ventricles were increased. An aortic root angiogram revealed a large tortuous right coronary artery that emptied into the right ventricular cavity. The diameter of this artery was 60 percent of the aortic root diameter (Fig. 2). The hemodynamic state deteriorated quickly after angiography. A sudden respiratory hemorrhage was followed by cardiac arrest.

Necropsy: At postmortem examination the heart was enlarged with a greatly dilated right ventricle and moderately enlarged right atrium. The left ventricle and left atrium were normal in size. A patent ductus arteriosus of moderate size was present and the foramen ovale was patent. The great vessels had a normal origin; the ascending aorta was moderately enlarged.

The coronary arteries had a normal origin, but the ostium of the right coronary artery was greatly dilated (diameter of 4.8 mm after fixation). The right coronary artery was dilated throughout its length. At its origin it left the atrioventricular groove and penetrated the upper anterior wall of the right ventricle, just below the anterior leaflet of the tricuspid valve (Fig. 3). The fistulous entry into the right ventricle measured 5 by 4 mm. The position of the fistulous entry into the right ventricle may have resulted in highly oxygenated blood streaming into the right atrium and superior vena cava. The ostium of the left coronary artery was normal.

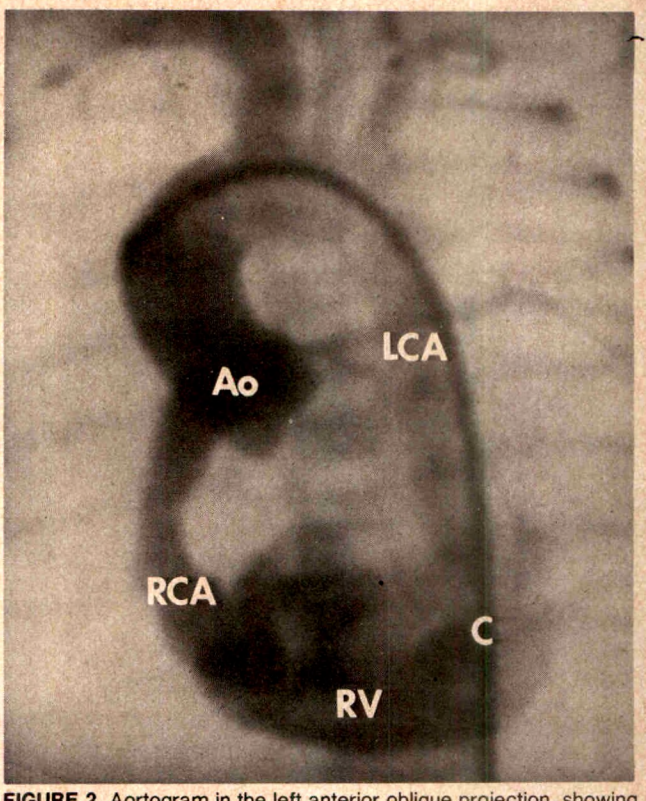

FIGURE 2. Aortogram in the left anterior oblique projection, showing the large right coronary arterial-right ventricular fistula. Ao = aorta; C = catheter; RCA = right coronary artery; LCA = left coronary artery; RV = right ventricular cavity.

TABLE I

Cardiac Catheterization Data*

Site	Pressures (mm Hg)	O_2 Saturation (%)
Superior vena cava	...	87
Inferior vena cava	...	64
Mid right atrium	*a* 14;*v* 14 (12)	78
Right ventricle	60/15	98
Pulmonary artery	60/30 (40)	95
Left atrium	*a* 17;*v* 19 (15)	100
Left ventricle	60/24	
Descending aorta	60/28 (40)†	88

*Catheterization carried out with patient breathing 100 percent oxygen.

† Figures in parentheses indicate mean pressure.

Discussion

Coronary arteriovenous fistulas generally exist as the only circulatory abnormality but may also be associated with other congenital abnormalities[3,4] with

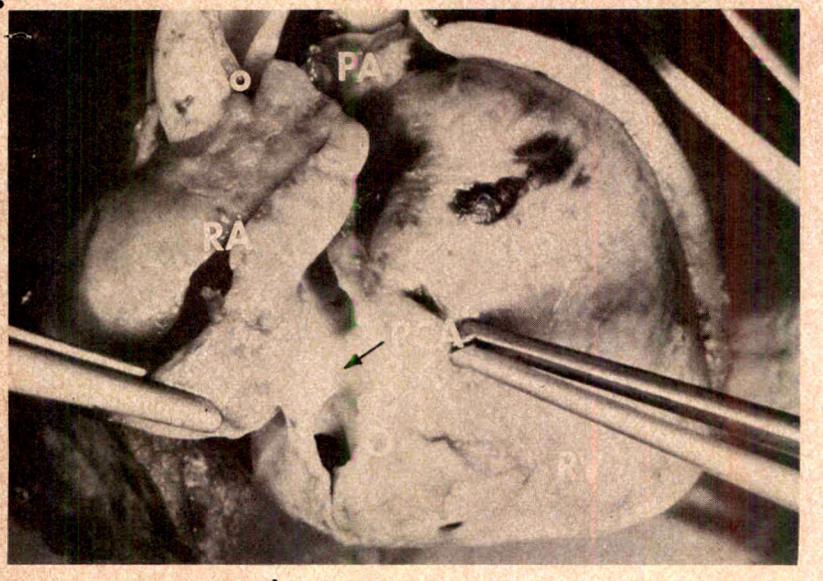

FIGURE 3. Specimen of heart showing the large coronary artery longitudinally, opening into the right ventricular cavity. The right atrium is moderately enlarged and the right ventricle is markedly dilated. Ao = aorta; O = fistulous opening into right ventricular cavity; PA = pulmonary artery; RA = right atrium; RCA = right coronary artery; RV = right ventricle.

severe stenosis or atresia of the semilunar valves. The embryogenesis of such a fistula depends on the persistence of wide intertrabecular spaces that, in the fetus, permit communication of the coronary arterial system with the cardiac cavities.[5] The same process is probably responsible for the diverticula and sinusoids that have been demonstrated in cases of pulmonary valve atresia with intact interventricular septum.[6]

When the coronary arteriovenous fistula is associated with other abnormalities, the course is determined predominantly by the primary disease. When it is the only circulatory abnormality the course is determined by the size and location of the shunt and the patient's age.[5] In the majority of reported cases, the shunt has been small and there has been no hemodynamic impairment. Consequently, most patients have been asymptomatic.[4,5,7–10] Congestive heart failure has been reported in only approximately 14 percent of cases.[11] It is most frequently found as the patient becomes older,[10,12–14] an observation that is consistent with the late development of heart failure in arteriovenous communications in other anatomic sites.[15] Coronary fistulas drain, in decreasing order of frequency, into the right ventricle, right atrium, pulmonary artery and coronary sinus.[16] Only a few cases of a fistula between a coronary artery and a left cardiac cavity have been described.[16] A fistula between a coronary artery and the coronary sinus is more likely than other fistulas to cause congestive heart failure (53 percent of 32 reported cases).[17]

Congestive heart failure has only rarely been reported in young infants with a coronary arteriovenous fistula. Cooley and Ellis[13] described three infants, aged 1 month, 6 weeks and 5 months, respectively, who tolerated heart failure for many months before surgery was undertaken. Gasul et al.[5] observed a 3 1/2 month old infant with dyspnea and marked cardiomegaly whose condition improved after surgical intervention at age 3 years. Daniel et al.[18] described a patient whose fistula between the left anterior descending coronary artery and the right ventricle resulted in congestive heart failure at age 1 month; operation at age 45 days was successful.

In our patient, refractory congestive heart failure developed shortly after birth. The refractoriness of the congestive heart failure was possibly due not only to the large left to right shunt but also to myocardial ischemia because oxygenated blood from the coronary artery may have been diverted to the fistula away from the myocardium.[3] Clinically, a large left to right shunt was evident. The echocardiographic study was helpful in excluding several anomalies that frequently cause congestive heart failure in neonates. The demonstration of two ventricles with a dilated anterior ventricle, two atrioventricular valves with normal characteristics and a dilated aorta ruled out left ventricular hypoplasia, right ventricular hypoplasia, single ventricle and tricuspid atresia. The dilated aorta made the diagnosis of an isolated ventricular septal defect unlikely. A dilated ascending aorta in cases of coronary arteriovenous fistula was previously noted by Gasul et al.[5] Although these echocardiographic findings could also be seen with a large patent ductus arteriosus, the septal motion was abnormal, indicating right ventricular volume overload, an atypical finding in patent ductus arteriosus. An unusual location of the left to right shunt was thus suspected, and the diagnosis was established by cardiac catheterization and angiography.

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Transmural Myocardial Infarction During Pregnancy

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Two young pregnant women with no known risk factors had a transmural myocardial infarction while they were lying in the supine position. Coronary arteriograms 3 1/2 and 4 months later, respectively, were normal. Coronary arterial spasm related to renin release from the transiently ischemic chorion is the proposed cause.

In the overwhelming majority of patients coronary arteriosclerosis is the underlying cause of acute myocardial infarction, and abnormal coronary arteriograms are the rule in these patients (99 percent in a recent series).[1] Factors other than organic obstruction may adversely influence coronary perfusion, creating an imbalance between requirements for oxygen and its availability.

There have been sporadic reports of transmural myocardial infarction in patients who were subsequently found to have normal coronary arteriographic studies.[2,3] We recently observed two young women who had an acute transmural myocardial infarction during the last trimester of pregnancy. Both patients subsequently had normal deliveries at term, and both had normal coronary arteriographic studies 3 1/2 and 4 months, respectively, after infarction.

Case Reports

Case 1: A 16 year old Mexican-American primipara with an expected date of confinement of February 4, 1972 was admitted to the Los Angeles County General Hospital on January 14, 1972 with a history of sudden severe and oppressive pain in the left side of the chest and both arms, in association with nausea, vomiting and diaphoresis. The symptoms began 4 days before hospitalization while she was lying down after doing housework. She gave no other history of previous cardiorespiratory difficulty, rheumatic fever, hypertension, renal disease or cigarette smoking. There was no family history of diabetes mellitus, heart disease, hypertension or vascular disease, but her mother died of pregnancy complications in Mexico.

Physical examination was normal; there were no third or fourth heart sounds. Values for hemoglobin, electrolytes, blood urea nitrogen, fasting blood sugar, Venereal Disease Research Laboratory test, bilirubin, lupus erythematosus preparation, serum cholesterol, phospholipids, triglycerides and total lipids were normal. The admission leukocyte count was 11,800 cells/mm^3. Serial creatinine phosphokinase and serum glutamic oxaloacetic transaminase studies were normal; lactic dehydrogenase levels were initially elevated but returned to normal in several days. Posteroanterior and lateral chest X-ray studies, arterial blood gases and a lung isotope scan on admission were normal. Serial electrocardiograms are shown in Figure 1; a vectorcardiogram was compatible with inferior wall infarction.

The patient was transferred to the Kaiser Foundation Hospital on February 11, for continued care relative to her pregnancy and had an uneventful delivery of a 3 kg normal boy on February 13. Coronary arteriograms and a left ventriculogram obtained on April 28 were normal.

Case 2: A 26 year old Caucasian woman in the 30th week of her second pregnancy gave a history of acute onset of dyspnea while she was watching television 4 days before hospitalization. Simultaneously she experienced se-

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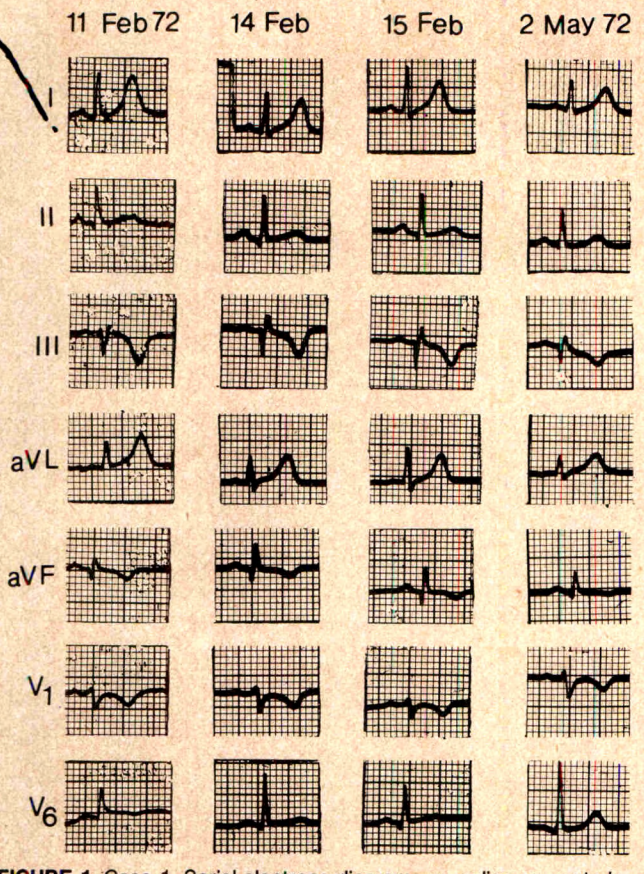

FIGURE 1. Case 1. Serial electrocardiograms revealing an acute inferior wall transmural myocardial infarction.

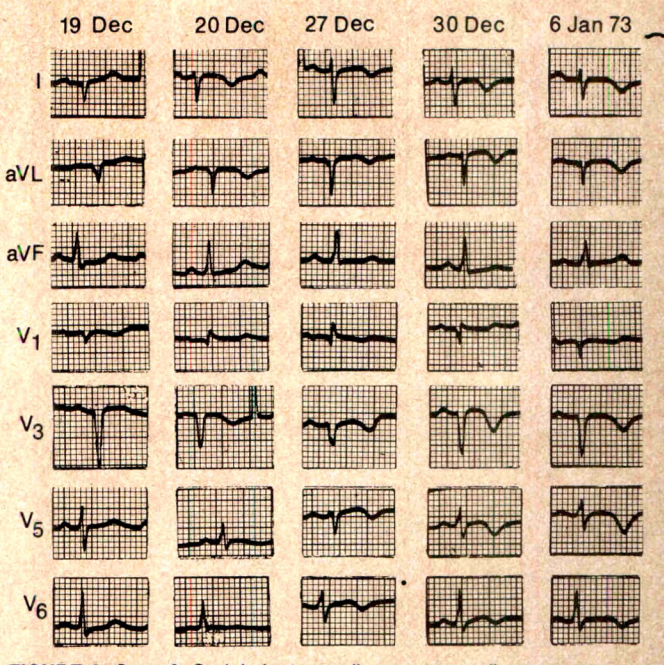

FIGURE 2. Case 2. Serial electrocardiograms revealing an acute anterior wall transmural myocardial infarction.

vere oppressive pain in the anterior area of the chest and neck and sought help at a neighbor's house where she had syncope and was taken by ambulance to the emergency room of another hospital. An electrocardiogram and chest X-ray film were obtained and the patient required endotracheal intubation because of respiratory arrest. She became asymptomatic and was discharged. On the day of admission to Kaiser Foundation Hospital on December 19, 1971 she again experienced severe retrosternal pain with radiation into the neck and lower jaw and a feeling of heaviness and discomfort in both arms while lying down. The electrocardiogram in our emergency room revealed an acute anterior wall myocardial infarction.

There was no prior history of chest pain or dyspnea. The first pregnancy, 2 years previously, was without complication, and she had no difficulty during the current pregnancy. The patient's mother died at age 54 years after cardiac surgery for mitral valve disease and coarctation of the aorta. There was no other family history of heart disease, hypertension, diabetes mellitus, thyroid disease, hyperlipoproteinemia or syphilis.

Physical examination was normal except for a transient third heart sound. Values for serum cholesterol, triglycerides and lipoprotein immediately and 3 months after myocardial infarction, hemoglobin, blood urea nitrogen, 3 hour glucose tolerance, creatinine, lupus erythematosus preparation and Venereal Disease Research Laboratory test were normal. The leukocyte count was 15,600 cells/mm^3 while serial serum enzyme studies were indicative of an acute myocardial infarction. Results of chest X-ray examination, arterial blood gas determinations, lung isotope scan, and viral study sera during the acute and convalescent period were also normal. Serial electrocardiograms are shown in Figure 2; serial vectorcardiograms were confirmatory of transmural anterior myocardial infarction. The patient was discharged after a 4 week uneventful course. She had a spontaneous, uneventful vaginal delivery on March 3.

Coronary arteriograms April 12, 1972 were normal (Fig. 3), and a left ventriculogram (Fig. 4) revealed anterior wall dyskinesis. Since October 1972 she has been symptom-free without medication.

Discussion

Myocardial infarction with normal coronary arteriograms: Among the causes suggested for normal coronary arteriograms in patients who have had a myocardial infarction are polycythemia, thrombocytosis, connective tissue disease, pulmonary emboli, hypotension, coronary arteriovenous shunting, anemia, aortic valve disease, dissection or aneurysm (or both) of coronary arteries, obstructive cardiomyopathy, syphilis and trauma.[4] These causes were ruled out in our two patients by history and physical and laboratory examinations. Metabolic abnormalities, small coronary vessel disease and impaired hemoglobin-oxygen diffusion have also been proposed.[5,6] Since the coronary circulation is least proficient at the endocardial and subendocardial levels,[7] these abnormalities tend to produce subendocardial ischemia rather than transmural myocardial infarction.[4] Another suggested cause, thromboembolism, is ruled out because with or without estrogen therapy,[4] abnormal coronary arteriograms are demonstrable in patients with this lesion, even when recanalization has occurred.[8,9] Spontaneous complete lysis of coronary arterial thromboemboli without a residual anatomic lesion has not been documented.[10] The use of oral contraceptive agents is associated with an increased incidence of venous thrombosis, pulmonary

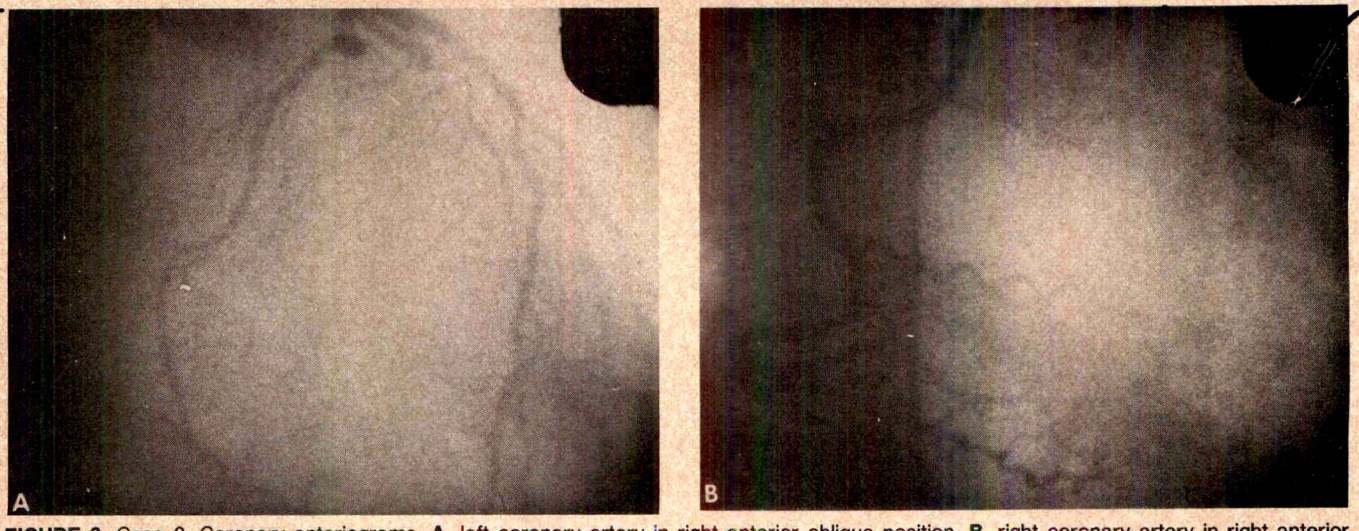

FIGURE 3. Case 2. Coronary anteriograms. **A,** left coronary artery in right anterior oblique position. **B,** right coronary artery in right anterior oblique position.

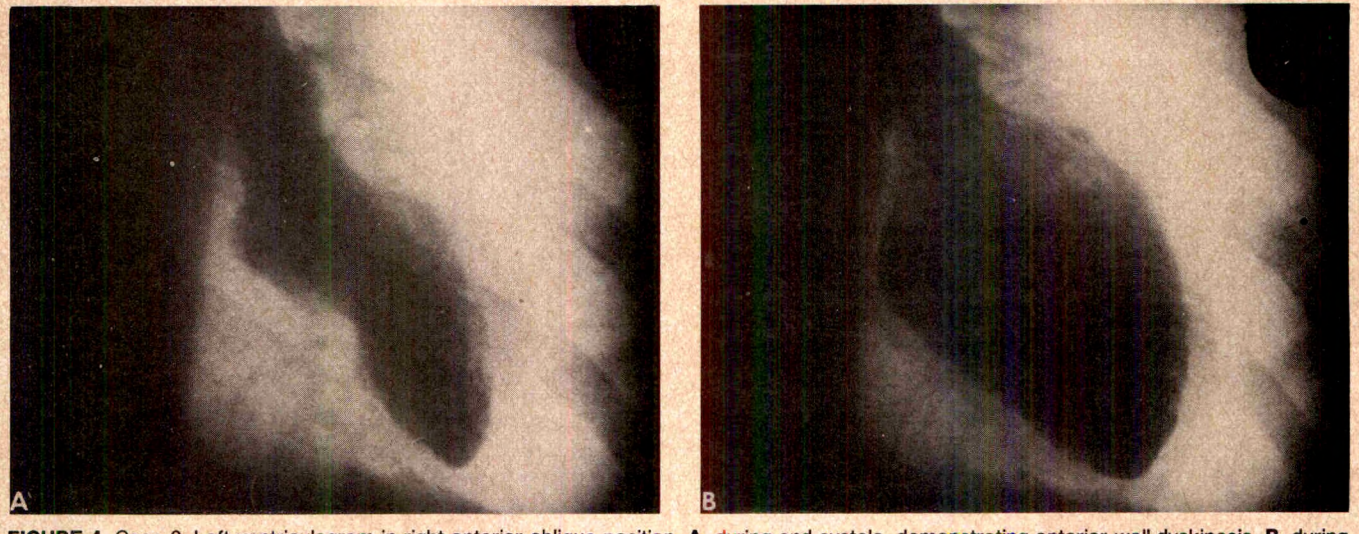

FIGURE 4. Case 2. Left ventriculogram in right anterior oblique position. **A,** during end-systole, demonstrating anterior wall dyskinesis. **B,** during end-diastole.

emboli and cerebral arterial thromboembolism, but not with increased incidence of myocardial infarction.[11] However, administration of large doses of estrogen in patients with prostatic carcinoma is associated with an increased incidence of cardiac and cerebrovascular deaths.[12] Normal coronary arteriographic studies have been found in patients with angina pectoris[13,14] or subendocardial infarction.[9,14,15–18] Neurocirculatory asthenia has also been implicated as a cause of chest pain in women with normal coronary arteriograms.[19]

Coronary arterial spasm: Spasm of coronary arteries, especially of the right coronary artery, can occur during coronary arteriography and usually can be resolved by sublingual administration of nitroglycerin or isosorbide dinitrate, or both.[1] Sphincter-like muscle has been demonstrated at the origin of the human right coronary artery.[20] Transmural myocardial infarction has occurred after apparent catheter-induced spasm of the left circumflex artery despite use of sublingually administered nitroglycerin and isosorbide dinitrate[21]; the patient had normal coronary arteriograms 3 months later. Nine of 200 patients with long-term industrial exposure to nitroglycerin had ischemic heart disease with chest pain and S-T changes on withdrawal from this exposure.[22] In one of these patients diffuse irregularity of the left anterior descending artery and two segmental narrowings of the right coronary artery were reversed by sublingual administration of nitroglycerin. Digital plethysmography also indicated digital arterial spasm. There are other cases of fatal cardiac ischemia related to withdrawal from industrial exposure to nitroglycerin in which postmortem study revealed normal coronary arteries.[23,24] Single cases and small groups of patients demonstrating transmural myo-

cardial infarction with normal or mildly abnormal coronary arteriograms performed 4 weeks to 9 years after myocardial infarction have been described.[2,3,9,10,17,19,25–31] Arteriograms in some of these reports show segmental smooth narrowings of coronary arteries suggestive of spasm.[19,25] The studies do not mention use of sublingually administered nitroglycerin or isosorbide dinitrate during the coronary arteriographic studies.

Prinzmetal's variant angina was originally thought to represent spasm in a main coronary artery[32] with partial atheromatous segmental occlusion. In one recent study of Prinzmetal's variant four of five patients had normal coronary arteriograms with one patient demonstrating reversible spasm of the right coronary artery and one having normal coronary arteries at postmortem examination.[33] In another report of Prinzmetal's angina, spasm in various areas of the right coronary artery during coronary arteriography caused transient inferior wall ischemia and heart block.[34] Upon relief of the attacks the coronary arteriograms were normal. Variant angina has also been precipitated by immersing the hand in cold water.[35]

Myocardial infarction in pregnancy: In two series, each reviewing about 40,000 deliveries, myocardial infarction during pregnancy was rare and seemed to occur more frequently in older multigravidae.[36,37] In one of these reports two of the three patients had a postpartum myocardial infarction.[37]

As in the study of Glancy et al.,[3] our patients had no history of angina prior to myocardial infarction. The coronary arteriograms were normal and showed all branches in both cases. In Case 1, the enzymes were first studied 4 days after chest pain, and it is not surprising that the creatinine phosphokinase and serum glutamic oxaloacetic transaminase levels were normal. Serum lactic dehydrogenase may be increased in 18 percent of normal pregnant women,[36,38] but the falling levels in Case 1 are in agreement with the electrocardiographic and vectorcardiographic changes of recent acute transmural inferior wall infarction. Our second patient had enzyme as well as electrocardiographic and vectorcardiographic changes confirmatory of acute transmural anterior wall infarction. Major coronary arterial atherosclerotic or thrombotic occlusion would be unlikely to clear completely in 4 months.

Mechanism: Although myocardial infarction has been documented during pregnancy,[36,37] pregnant women rarely undergo coronary arteriography. The chest pain in both of our patients occurred while they were lying in the supine position during the 3rd trimester of pregnancy, past the time of maximal hemodynamic stress of pregnancy. The supine position in the 3rd trimester of pregnancy decreases uterine blood flow,[39] as well as inferior vena caval venous return to the heart. The uterus is the site of renin production in the anephric woman,[40] and the human chorion contains 160 times the renin concentration of maternal plasma.[41] The hypertension of preeclampsia is of humoral rather than neurogenic origin,[42] and the abnormally increased pressor response to angiotensin, norepinephrine and epinephrine precedes by up to 3 months the development of hypertension in pregnant women.[39,43]

Thus, all but one of the previously proposed causes for transmural myocardial infarction with normal coronary arteriograms have been ruled out. The transient physiologic setting in which prolonged supine recumbency leads to uterine renin release and angiotensin production causing coronary arterial spasm was present. Although our hypothesis is speculative, we suggest that prolonged but reversible coronary arterial spasm is the most likely of the previously proposed mechanisms for the myocardial infarction in our two patients.

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NOREPINEPHRINE

Role of short-range transmitters in hypothalamic activities. Endröczi E. **J Neural Transm Suppl 11(0):213-25, 1974 (22 ref.)**

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Monoamines and the regulation of vigilance and sleep. Putkonen PT. **Med Biol 52(3):193-9, Jun 74 (68 ref.)**

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A contribution of intracavitary electrocardiography to the differential diagnosis of right ventricular diastolic restriction syndrome. Maia IG, et al. **Am Heart J 88(4):401-7, Oct 74 (36 ref.)**

PHOSPHOLIPIDS

Drug-induced phospholipidosis. Lüllmann H, et al. **Ger Med 3(3-4):128-35, Winter 73 (38 ref.)**

POLYCYTHEMIA VERA

The polycythemias and their relationship to erythropoietin. Jacob HS. **DM 0(0):3-26, Aug 74 (24 ref.)**

PULMONARY CIRCULATION

Mechanisms underlying vasomotor regulation of regional pulmonary blood flow in normal and disease states. Bergofsky EH. **Am J Med 57(3):378-94, Sep 74 (60 ref.)**

Pharmacokinetic function of the pulmonary circulation. Bakhle YS, et al. **Physiol Rev 54(4):1007-45, Oct 74 (262 ref.)**

Pulmonary blood flow in normal and abnormal states. Racz GB. **Surg Clin North Am 54(5):967-77, Oct 74 (32 ref.)**

Microscopic studies of the pulmonary circulation in situ. Webb WR, et al. **Surg Clin North Am 54(5):1067-76, Oct 74 (26 ref.)**

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The mechanisms of Raynaud's phenomenon: Part 2. McGrath MA, et al. **Med J Aust 2(10):367-75, 7 Sep 74 (106 ref.)**

SEROTONIN

Relation of biogenic amines to aggressive behaviour. Johansson G. Med Biol 52(3):189-92, Jun 74 (33 ref.)
Monoamines and the regulation of vigilance and sleep. Putkonen PT. Med Biol 52(3):193-9, Jun 74 (68 ref.)

SHOCK, ENDOTOXIC

Respiratory system in experimental endotoxic shock. II. Morphological investigations and physiopathology of pulmonary disturbances. Brodzińska K. Anaesth Resusc Intensive Ther 1(4):277-304, Oct-Dec 73 (112 ref.)

THROMBOPHLEBITIS

Variations of heparin therapy for thromboembolic disease. Marder VJ. Med Clin North Am 58(5):1121-8, Sep 74 (24 ref.)
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Phlebography in the diagnosis of acute deep venous thrombosis of the legs and pelvis. De Reus HD. Radiol Clin Biol 43(6):549-58, 1974 (35 ref.)

VAGUS NERVE

Sympathetic-parasympathetic interactions on the ventricular myocardium: possible role of cyclic nucleotides. Schwegler M. Basic Res Cardiol 69(3):215-21, May-Jun 74 (37 ref.)

VASCULAR DISEASES

Ophthalmic manifestations of systemic vascular disease. Cogan DG. Major Probl Intern Med 3(0):1-187, 1974 (709 ref.)
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VASODILATOR AGENTS

Candidate hormones of the gut. V. Vasoactive intestinal peptide (VIP). Said SI. Gastroenterology 67(4):735-7, Oct 74 (18 ref.)

VASOMOTOR SYSTEM

Mechanisms underlying vasomotor regulation of regional pulmonary blood flow in normal and disease states. Bergofsky EH. Am J Med 57(3):378-94, Sep 74 (60 ref.)

VENA CAVA, SUPERIOR

Idiopathic dilatation of the superior vena cava (IDSVC). Polansky S, et al. Pediatr Radiol 2(3):167-74, 1974 (13 ref.)

VENTRICULAR FIBRILLATION

Editorial: Primary ventricular fibrillation. Pantridge JF, et al. Eur J Cardiol 1(4):335-7, Apr 74 (45 ref.)

WOLFF-PARKINSON-WHITE SYNDROME

The Wolff-Parkinson-White syndrome anno 1973. Durrer D, et al. Eur J Cardiol 1(4):347-67, Apr 74 (90 ref.)

BOOK REVIEWS

MANUAL ON ARTIFICIAL ORGANS. VOLUME 2: THE OXYGENATOR, by Yukihiko Nosé. St. Louis, Missouri, C. V. Mosby, 1973, 350 pages

A very attractive book with large pages, aesthetic use of open space, legible type, plentiful clear illustrations, sensible subdivision of text by bold headings, and an easily read and understood prose style, this text contains a wealth of up to date detail and a very comprehensive and quite well referenced bibliography. The author has attempted to find a middle ground between a simple how to do it text on perfusion for open heart surgery and a purely academic exposition. Although he has succeeded well enough so that the volume is valuable and will be useful to many, there are several unfortunate consequences. Important areas of controversy are glossed over, criticism is muted and the reader will not find the information needed to assist in making decisions about equipment and perfusion techniques. For example, the vastly complex problem of postperfusion neurologic damage is presented as simply a consequence of emboli: "Probably filtering out all particles greater than 25 microns will prevent these neurologic complications." The role of platelet activation and clumping in the body, release of vasoactive materials, disseminated intravascular coagulation, fat embolization due to colloid instability and many other possibilities are thus dismissed as causes of neurologic damage. Certainly this intellectual mediocrity is not intentional, but it does result in a simplistic presentation and detracts from an otherwise very admirable book.

The reader will find an excellent historical perspective and strong chapters on the different types of oxygenators, pulsatile and nonpulsatile pumps, methods of perfusion and the clinical management of cardiopulmonary bypass. The emphasis is on oxygenators of all types, including newer membrane varieties, with meticulous detail concerning their use as well as information on circuits, fittings and all accessory equipment. There is much good background material on physiology and related subjects, although the presentation is perhaps long on descriptive detail and too brief on comparison. There are some unfortunate errors and omissions; heparin doses are given in milligrams although this drug is always standardized and labeled by units. This error simply perpetuates a serious but common mistake of the cardiovascular team. The Lee-White time (glass clotting time) is the only method mentioned for following heparin effect even though the development of more rapid and reproducible tests is now of intense interest in the field (for example, the partial thromboplastin time and the activated clotting time).

Although this volume cannot be recommended as a primary or sole source of information on the oxygenator, it fulfills a real need and should be made widely available as a teaching aid for students, residents and pump technicians. The arrangement of material is especially suited for didactic instruction and will thus also prove useful to those responsible for training all the members of the cardiovascular team.

E. Converse Pierce, II, MD
Bronx, New York

The President's Page: Goals and Objectives

You have honored me by electing me your President and I will do my best to live up to your expectations. I would like to take this opportunity to share with you some of my expectations for the College.

It is an undisputed fact that the College in 1975 is an important and integral part of American, and for that matter, worldwide cardiology, and the recognized leader in cardiovascular postgraduate education. This has been accomplished in its first 25 years—a phenomenal accomplishment.

As we look forward to the next 25 years, we see a changing medicine and, with it, a changing cardiology. It is my expectation that we will become active participants in these changes and not stand by idly, reacting only to already accomplished facts, facts that may have been forced upon us by others whose interest in cardiology may be secondary and often subservient to some overriding social or political issue.

It is my expectation that we will face up to the nation's manpower needs for cardiovascular practice, both quantitatively and qualitatively. This will require a greater interest in the economics of cardiology and legislative involvement.

It is my expectation that we will be leaders in quality cardiovascular practice and that we will do this foremost and always by example, in order that our qualifications for leadership remain unquestioned.

It is my expectation that we will continue to support research, basic and clinical, and the research environment, in the recognition that without new knowledge and new insight, delivery of health care will rapidly become a meaningless slogan.

The College is uniquely prepared to deal with these challenges and to provide the vehicle by which our expectations can be reached. We are a young organization; 25 percent of our membership is 40 years of age or less. We are a qualified organization, our fellowship requirements being those of competence and purpose. Our administrative staff is capable and effective, and the administrative mechanism flexible and so structured that it can respond promptly to changes affecting our specialty.

It is clear that these expectations will require a departure from the traditional role of the College as primarily an educational organization, while at the same time maintaining the educational leadership assured in part by the reality of Heart House. Such changes facing the College are fundamental and very complex and involve more than rhetoric. In order to ensure that my expectations, and yours, are essentially the same, a committee will soon be appointed to deal with the *goals and objectives* of the College. On the basis of this committee's deliberations, as guided by the membership, I hope to be in a position to report to you when my term of office ends that significant progress has been made toward ensuring a leadership role for the College. To accomplish this, and to guide the deliberations of the Goals and Objectives Committee, we need your support. Please let us know what your expectations are for your College.

Charles Fisch, MD, FACC
President
American College of Cardiology

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and various other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education in the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

MAR. 6–8 **Cardiovascular Disease—1975: Practical Diagnosis and Management.** John Ross, Jr., FACC, Robert A. O'Rourke, FACC, Joel S. Karliner, FACC and Kirk L. Peterson, FACC, directors. Sheraton Harbor Island Hotel, San Diego, Calif.

MAR. 13–14 **Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** James S. Forrester, H. J. C. Swan, FACC and Kenneth I. Shine, directors. Cedars of Lebanon Hospital, Los Angeles, Calif.

MAR. 17–20 **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. The Children's Hospital, Children's Hospital Medical Center, Cincinnati, Ohio.

MAR. 24–28 **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

APR. 7–16 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Sante Fe Inn, Rancho Sante Fe, Calif.

APR. 14–18 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Richard Gorlin, FACC, Michael V. Herman, FACC and Louis E. Teichholz, co-directors. Mount Sinai Medical Center, New York, N.Y.

APR. 16–18 **Echocardiography for the Clinician.** Joseph K. Perloff, FACC, Nathaniel Reichek and Morris N. Kotler, FACC, directors. The University of Pennsylvania Medical Center, Philadelphia, Pa.

APR. 22–24 **Optimal Standards of Care in Cardiac Emergencies.** Albert N. Brest, FACC, director, Holiday Inn, Philadelphia, Pa.

APR. 30 to MAY 2 **Core Curriculum: Vectorcardiography: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

MAY 5–8 **Current Concepts in Cardiology—1975.** Philip R. Akre, director and Masato Takahashi, FACC and John A. Bowers, co-directors, Caesars Palace, Las Vegas, Nev.

MAY 10–11 **Core Curriculum: Clinical Vectorcardiography 1975.** Irwin Hoffman, FACC and Robert I. Hamby, FACC, directors. Americana Hotel, New York, N.Y.

MAY 12–15 **Cardiology for the Internist.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 16–18 **Core Curriculum: Myocardial Biology in Health and Disease—1975.** Arnold Schwartz, FACC and Mark L. Entman, directors. Holiday Inn-Medical Center, Houston, Tex.

MAY 29–31 **Ischemic Heart Disease: A Critical Overview.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Golden Gateway Holiday Inn, San Francisco, Calif.

JUNE 4–7 **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

JUNE 5–7 **Progress in Coronary Artery and Valvular Heart Disease.** S. H. Rahimtoola, FACC, director, Benson Hotel, Portland, Ore.

AUG. 23–25 **Tutorials in the Tetons (Cardiac Emergencies).** Robert S. Eliot, FACC, director and Robert J. Davis, FACC, Alan D. Forker, FACC, Vincent F. Miscia, FACC and Gerald L. Wolf, co-directors. Grand Teton National Park, Moran, Wyo.

New Members Elected

The following individuals were elected to membership in the American College of Cardiology on October 15, 1974, in the category indicated.

Fellowship

ALVES, Larry E., MD, Illinois
AMIDI, Morteza, MD, Iran
APPEL, Saul B., MD, Texas
ARAVINDAKSHAN, Vadakepat, MB, Kentucky
ARNON, Rica G., MD, Tennessee
BERGER, Stephen M., MD, Ohio
BLOMQVIST, C. Gunnar, MD, Texas
BRINK, William R., MD, Pennsylvania
BRUNDAGE, Bruce H., MD, District of Columbia
CAPONE, Robert J., MD, Rhode Island
CASHION, William R., Jr., MD, Texas
CHIA Boon Lock, MB, Republic of Singapore
CHIANG, Benjamin N., MD, Taiwan
CHOUGH, Cheen B., MD, Pennsylvania
COLLENS, Richard, MD, New York
COOPER, Jerome A., MD, New York
DEUTSCHER, Robert N., MD, California
EBER, Leslie M., MD, California
FOX, Arthur C., MD, New York
FRANTZ, Stephen L., MD, New York
FRUEHAN, C. Thomas, MD, New York
FUNK, David C., MD, Iowa
GAULDEN, Edmund C., MD, California
GERSONY, Welton M., MD, New York
GILLIS, John G., MD, Canada
GLASSMAN, Ephraim, MD, New York
GOLDREYER, Bruce N., MD, California
GREATBATCH, Wilson, BEE, MS, New York
GUY, Clifford R., MD, Florida
HABAK, Philip A., MB, Iowa
HALLAL, F. Joseph, MD, District of Columbia
HILL, J. Donald, MD, California
HURST, Victor W., III, MD, Connecticut
KAMADA, Roy O., MD, Hawaii
KASSER, Irwin S., MD, California
KELLY, Paul B., Jr., MD, California
KRAVITZ, Alan E., MD, Georgia
LANIADO, Shlomo, MD, Israel
LEE, T. David, Jr., MD, Oregon
LEVIT, Samuel M., MD, Pennsylvania
LIE, Jauw Tjen, MD, Texas
MASSIN, Edward K., MD, Texas
MEISTER, Steven G., MD, Pennsylvania
MILLS, Noel L., MD, Louisiana
MISCIA, Vincent F., MD, Nebraska
O'KEEFE, James D., MD, Texas
OXMAN, Herbert A., MD, Tennessee
PARASKOS, John A., MD, Massachusetts
RABKIN, Simon W., MD, Canada
RATER, David A., MD, Iowa
RUBIN, Joseph W., MD, Georgia
RUSSO, John V., MD, District of Columbia
SAPHIR, J. R., MD, California
SCHEIDT, Stephen S., MD, New York
SCHLOFF, Leonard D., MD, Minnesota
SCOTT, James I., Jr., MD, Ohio
SIMPSON, Carroll S., MD, Washington
SIMPSON, James W., MD, Texas
SLESAR, Stephen J., MD, Canada
STEEG, Carl N., MD, New York
TAYLOR, Jack B., MD, District of Columbia
THOMAS, Harry M., Jr., MD, Hawaii
TREASURE, Robert L., MD, Texas
TROUT, Kenneth W., MD, New York
van den BROEK, Hans, MD, New Jersey
VANHOUTTE, Paul M., MD, Belgium
WAGNER, Stanley C., MD, New York
WEERASENA, Mahinda, MB, Sri Lanka
WILLIAMS, Troy H., MD, Texas
WILSON, W. Stan, MD, Montana
WISOFF, B. George, MD, New York
ZAVER, Alla G., MB, Massachusetts

Advanced to Fellowship

AGRUSS, Neil S., MD, Illinois
CHENG, Simon, MD, California
DONMOYER, Theodore L., MD, Pennsylvania
FRIEDMAN, Howard S., MD, New York
GALYEAN, James R., III, MD, Mississippi
HERNANDEZ, Antonio, Jr., MD, Missouri
JAYARAMAN, Kalarikkal K., MD, Louisiana
KERZNER, Jay S., MD, Florida
MARTIN, C. Edwin, MD, Pennsylvania
MOHIUDDIN, Syed, MD, Nebraska
OEHLERT, William H., Jr., MD, Oklahoma
POPP, Richard L., MD, California
ROWEN, Howard E., MD, Ohio
SCHWIMMER, Julius, MD, Arizona
SWAN, David A., MD, California
WEINRAUCH, Harry, MD, New York
WILENSKY, Allan S., MD, Alabama

Associate Fellowship

ALPERT, Joseph S., MD, California
BHATT, Dilip R., MD, California
BUCHANAN, Robert A., Jr., MD, North Carolina
CARRILLO-Leon, Fermin A., MD, Venezuela
CURRY, Rupert C., Jr., MD, Florida
DAS GUPTA, Ramanuja, MB, Maryland
ESLAMI, Bahram, MD, Iran
EYBEL, Carl E., MD, Ohio
FRANCIS, John E., MD, Michigan
JAFERI, Ghanzanfar A., MB, New Jersey
JELINEK, V. Michael, MD, Australia
*LOMNITZ, Esteban R., MD, New Jersey
MARABOYINA, Sudnakar, MD, Ohio
MAZURKIE, Stanley J., MD, Massachusetts
MISHRA, Surendra, MD, India
MYERS, Richard W., MD, California
*OSCHERWITZ, Mark, MD, California
*PHILLIPS, William J., MD, Missouri
*POOYA, Manoochehr, MD, District of Columbia
QUINTERO-Rodriguez, Luis R., MD, Mexico
RABINOWITZ, Robert J., MD, New York
ROMNEY, David, MB, Canada
SAHGAL, Kamal K., MD, Minnesota
STICKLEY, Louis P., Jr., MD, Missouri
SUKERMAN W., Moises, MD, Venezuela
THEODOSIOU, George, MD, Massachusetts
VARMA, Amrit S., MD, India

Advanced to Associate Fellowship

KAMENEAR, Harold R., MD, Illinois
KINHAL, Vithal, MD, Michigan
VALENTI, Nicolas T., MD, Florida
WACHEN, Robert, MD, New York

Affiliates

BANAAG, Benjamin B., MD, California
*CINTADO, Luis J., MD, Florida
CRELINSTEN, Gordon L., MD, Canada
*DANIELS, David H., Jr., MD, District of Columbia
*FUTRAL, Allen A., Jr., MD, Virginia
ISLEY, Patricia E., MD, California
KINO, Masaya, MD, Massachusetts
*LEVIN, Edward N., MD, California
MILLS, Roger M., Jr., MD, Massachusetts
MURRAY, Michael E., MD, Illinois
*REEVE, F. Joan Sakai, MD, California
SHAHAMATPOUR, Ahmad, MD, Ohio
*SILBERMAN, Richard E., MD, Wisconsin

* Elected July 18, 1974

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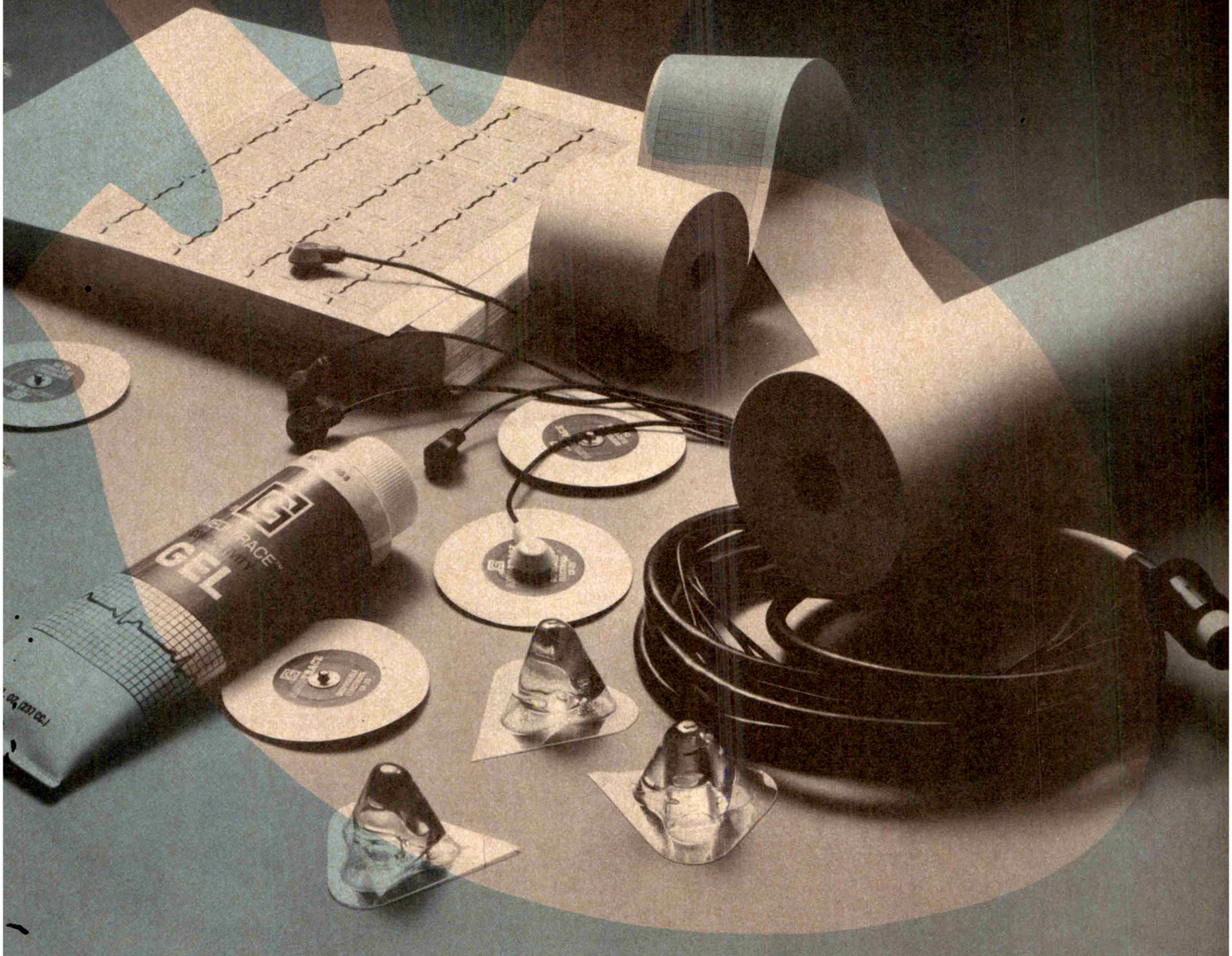

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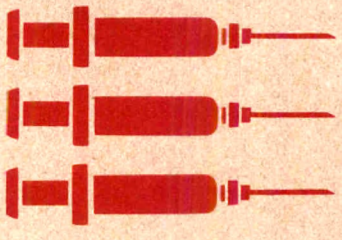
Effectiveness...

I.V. Administration Guidelines for Premature Ventricular Contractions and Tachycardia

1. Preparation of drug: Dilute before I.V. use.
2. Usual dosage range: 200-1000 mg.
3. Infusion rate: Not to exceed 25-50 mg. per minute. Total I.V. dose not to exceed 1000 mg.
4. Precautionary measures:
   a. Keep patient in supine position.
   b. Monitor electrocardiographically and discontinue if myocardial toxicity is evidenced.
   c. Measure blood pressure almost continuously and temporarily discontinue infusion if blood pressure falls more than 15 mm. Hg.

When therapeutic blood levels are required quickly, I.V. Injections

100 mg. every 5 minutes until arrhythmia suppressed (up to a maximum dose of 1 gram).



For ventricular arrhythmias

SQUIBB® 'The Priceless Ingredient of every product is the honor and integrity of its maker.'™

A64

by a variety of routes

I.V. Infusion

2-6 mg. per minute[1].
(42.8 μg./min./kg.)[2]

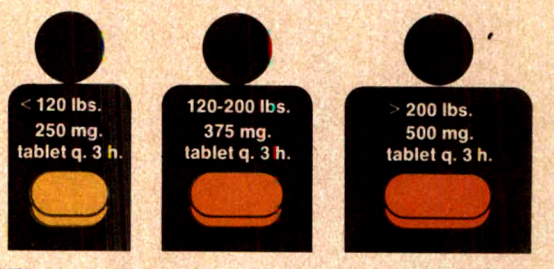
1. Wyman MG, Hammersmith L: Am J Cardiol 33:661-667, 1974
2. Bigger JT, Jr., Giardina EV: MCV Quart 9 (1): 65-76, 1973

Terminate I.V. infusion *4 hours before* oral regimen begun.

Oral Administration Guidelines to Provide 50 mg./kg./day* for Ventricular Arrhythmias

Ventricular Tachycardia
(give priming dose of 1 g. if patient has not received prior infusion)

Premature Ventricular Contractions



*This dosage schedule is for use as a guide for treating the average patient, but all patients must be considered on an individual basis.

Pronestyl®
(Procainamide Hydrochloride)
through the entire therapeutic course

See next page for brief summary.

(Procainamide Hydrochloride Tablets)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100.

PRONESTYL® INJECTION (Procainamide Hydrochloride Injection U.S.P.)

Description: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml. © 1974 E. R. SQUIBB & SONS, INC. 444-009

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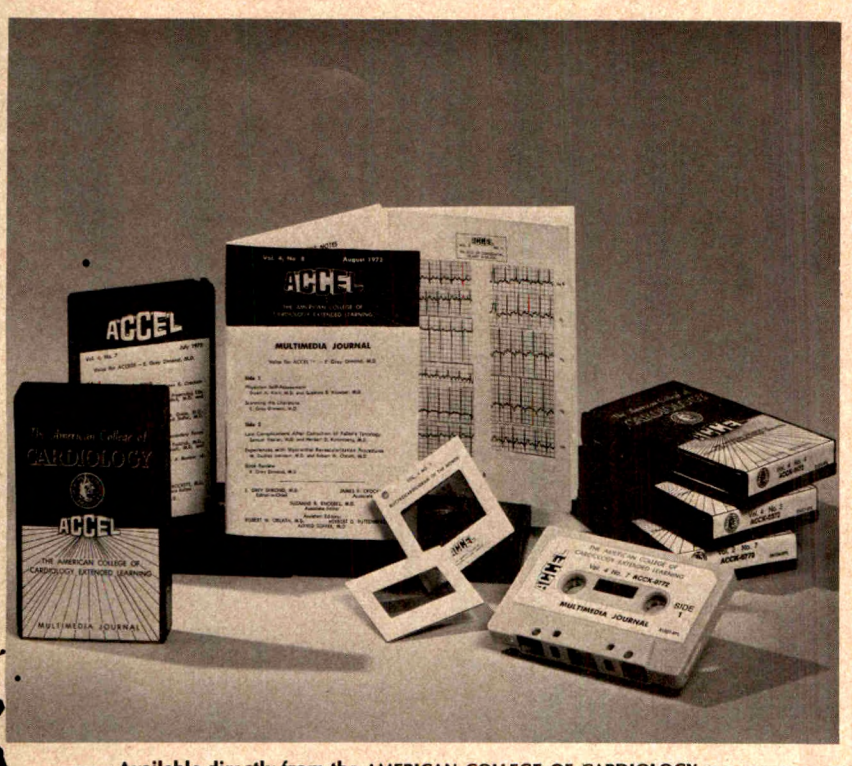

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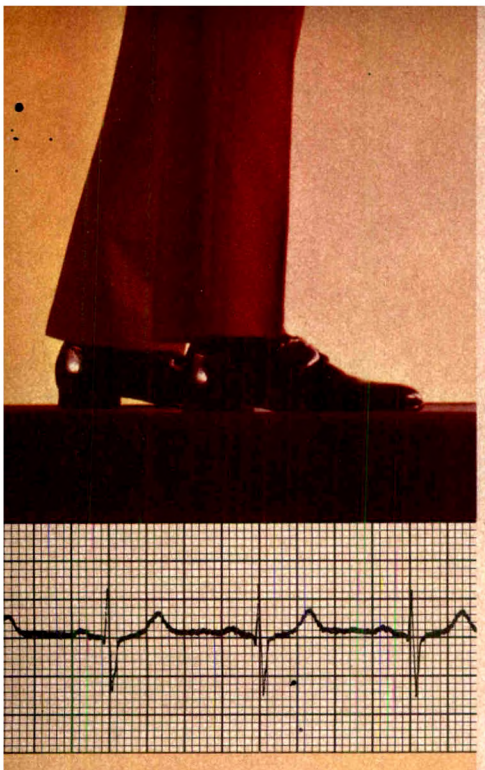
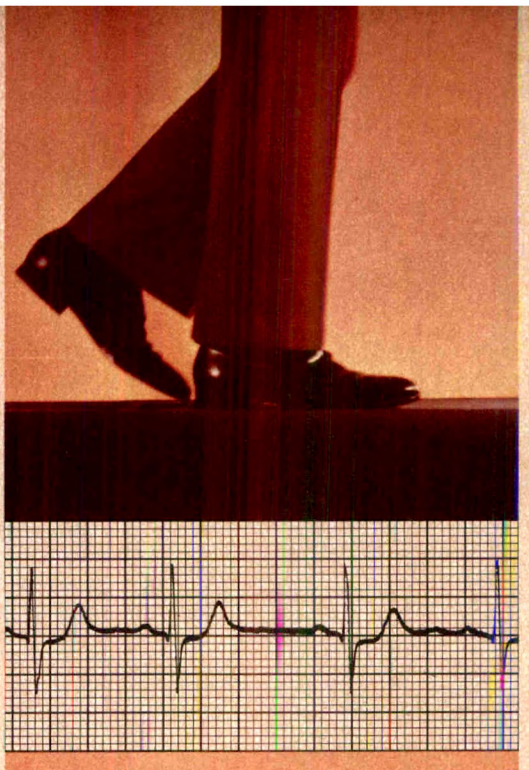
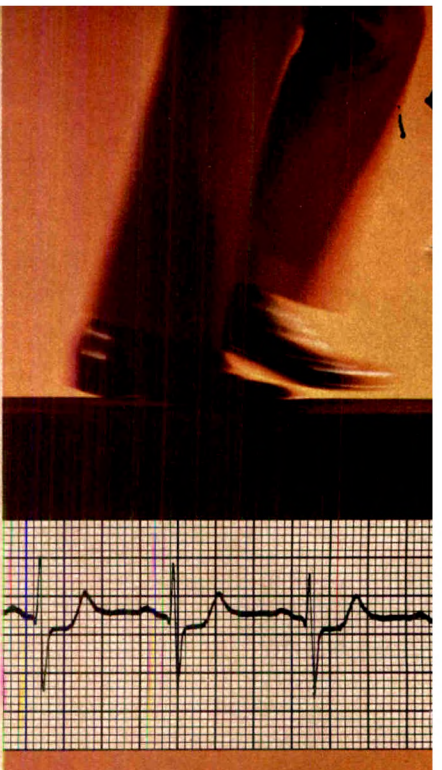


Standing, at rest, V-5, HR-74. American's Stress Test Electrode supplies immediate base line stability. Testing with a narrow, drift free base line can begin as soon as the self-adhering, silver/silver chloride electrodes have been applied to the patient and connections made to your monitoring equipment.



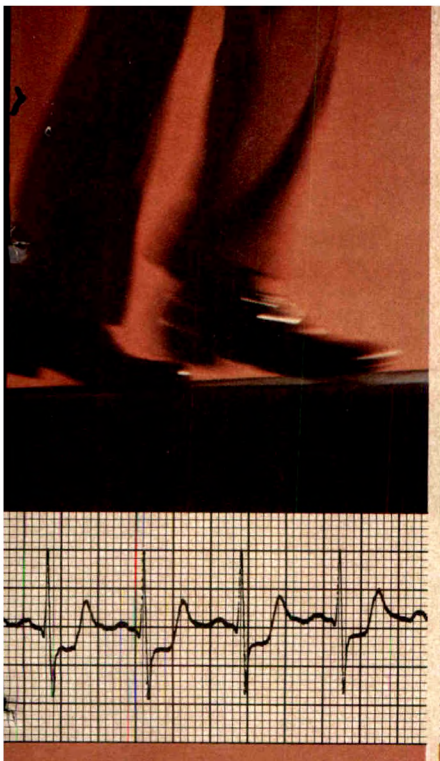
4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and impregnated foam pad which is slightly oversize to assure positive, continuous pressure at the electrode-skin surface. The results: immediate onset and virtual elimination of base line instability and motion artifact.



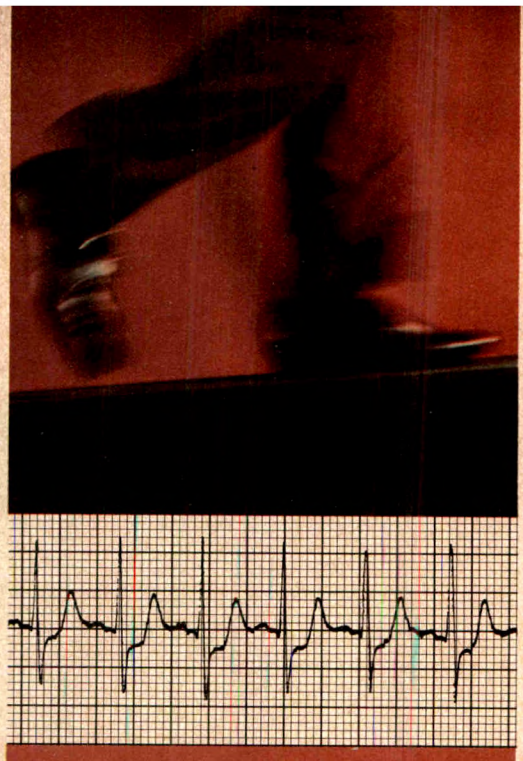
4th Minute at 3 mph (8th minute o test), 0% Grade, V-5, HR-83. (Th patient's ECG indicates 1 mm of S depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interferen that might otherwise mask small amounts of S-T depression.

Finally.

An electrode/cable system specifically designed for stress testing.

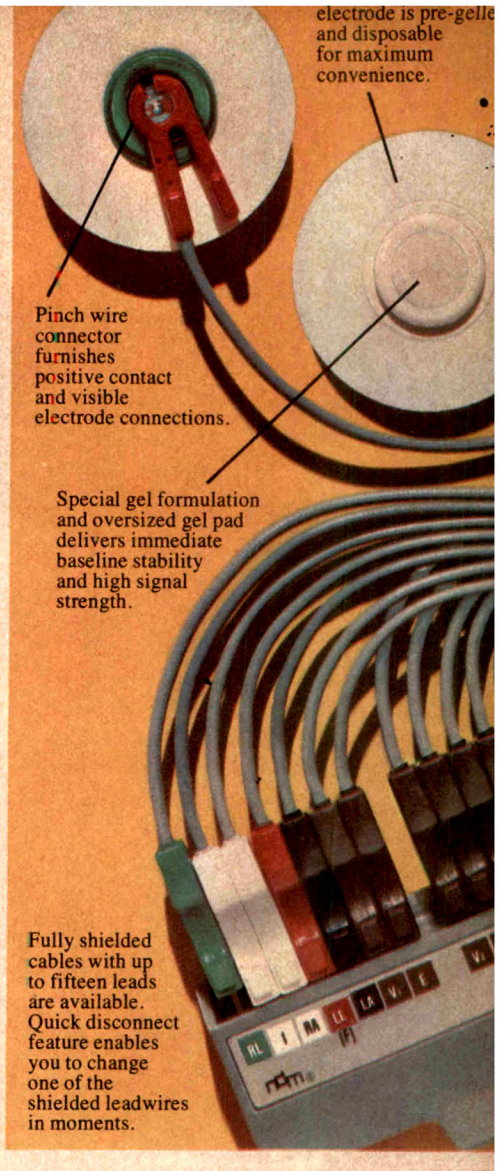


Minute at 3 mph (12th minute
est), 5% Grade, V-5, HR-117.
T depression increases to 2.5 mm.)
n at high work loads, the Ameri-
Stress Test Electrode and fully
lded cable system delivers a stable
line and noise-free signal.



4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.)
Long test procedures* seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

* Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's new Stress Test Electrode and fully shielded cable system.

If you've been diagnosing from stress test electrocardiograms that display wide or unstable base lines, severe motion artifact or possible hidden S-T depression, please contact us. We think we can help.

*Examples shown were produced under clinical conditions during an actual stress test procedure using the American Stress Test Electrode system.

We invite you to try the only electrode/cable system designed to match the "no compromise" nature of exercise stress testing. The fully shielded patient cable is adaptable to your present monitoring equipment, regardless of its make.

Please contact your American Hospital Supply or NDM representative and ask for:

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Peritrate® SA Sustained Action

(pentaerythritol tetranitrate) 80 mg

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

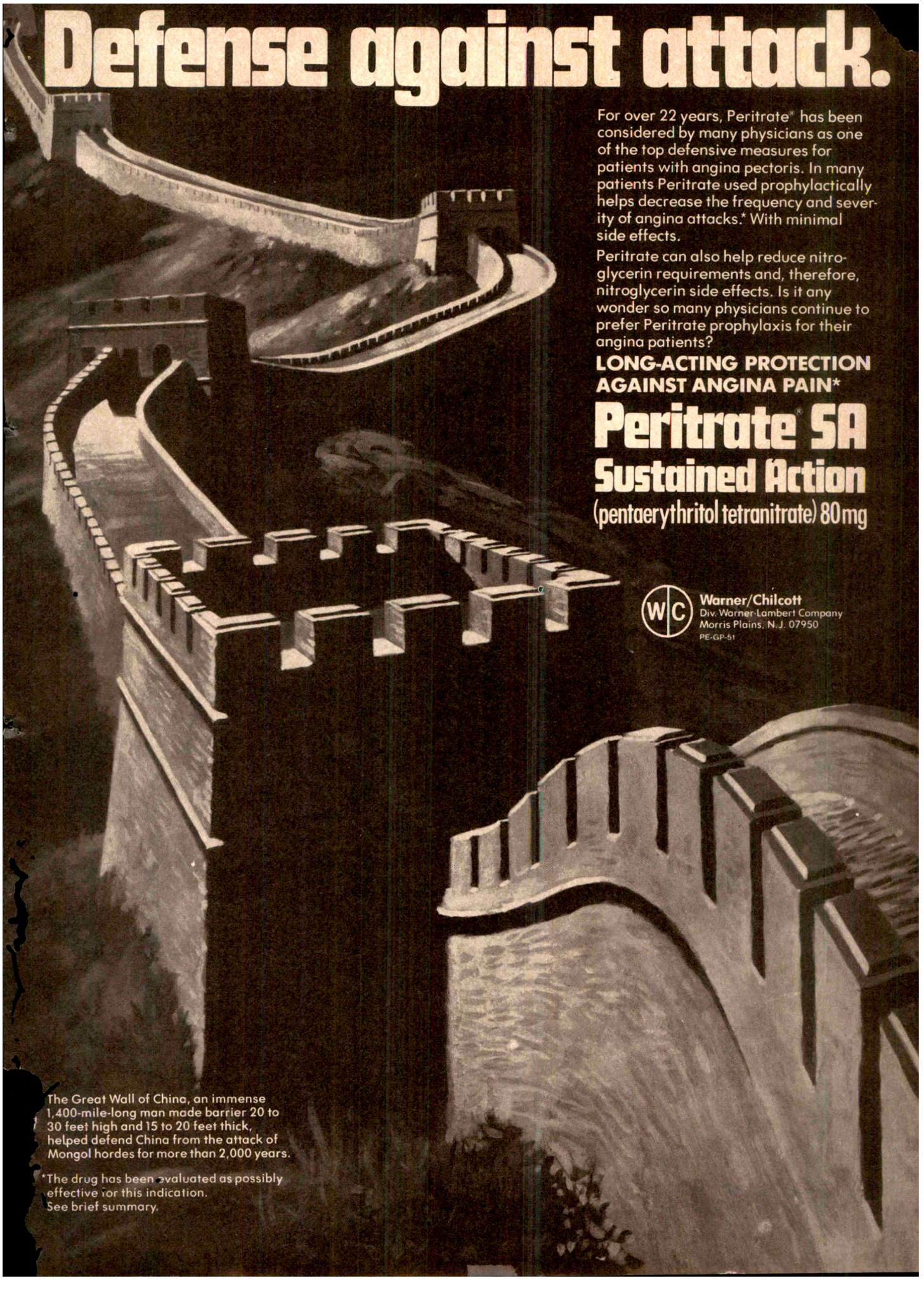
Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.



For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

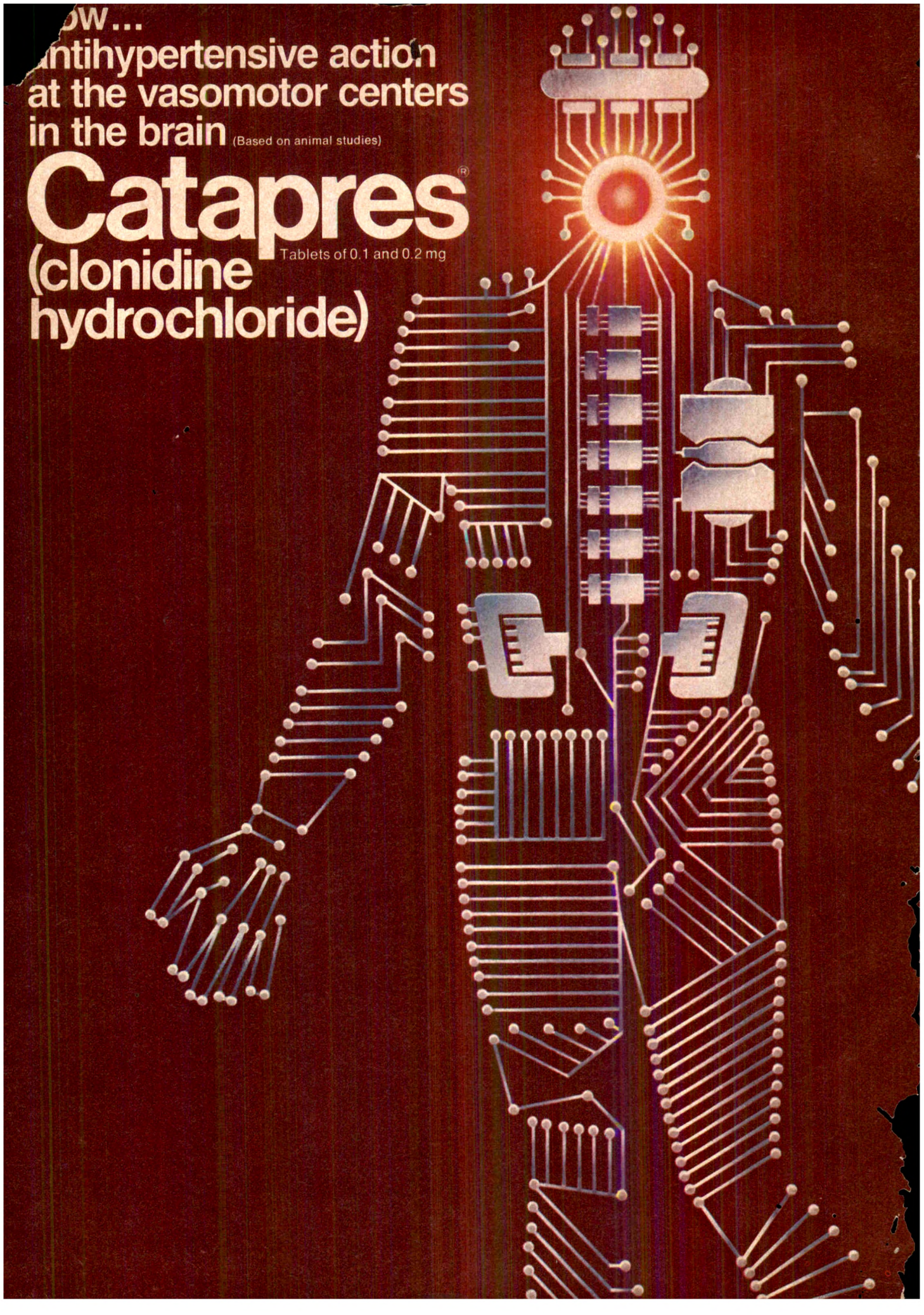
LONG-ACTING PROTECTION AGAINST ANGINA PAIN*

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) 80 mg

Warner/Chilcott
Div. Warner-Lambert Company
Morris Plains, N.J. 07950
PE-GP-51

The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary.


ow...
ntihypertensive action
at the vasomotor centers
in the brain (Based on animal studies)
Catapres®
Tablets of 0.1 and 0.2 mg
(clonidine
hydrochloride)

Central action

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardioaccelerator and vasoconstrictor centers in the medulla.

Not a "depleter", blocker", "inhibitor" or false transmitter"

Not a rauwolfia

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Elmsford, New York 10523

Effective in hypertension, mild to severe

Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

Renal blood flow and glomerular filtration rate essentially unchanged

Mild to moderate potency

The most common side effects are dry mouth, drowsiness and sedation. These generally tend to diminish with continued therapy. Other potential adverse reactions are listed in the Brief Summary.

Catapres® (clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established). These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride.

Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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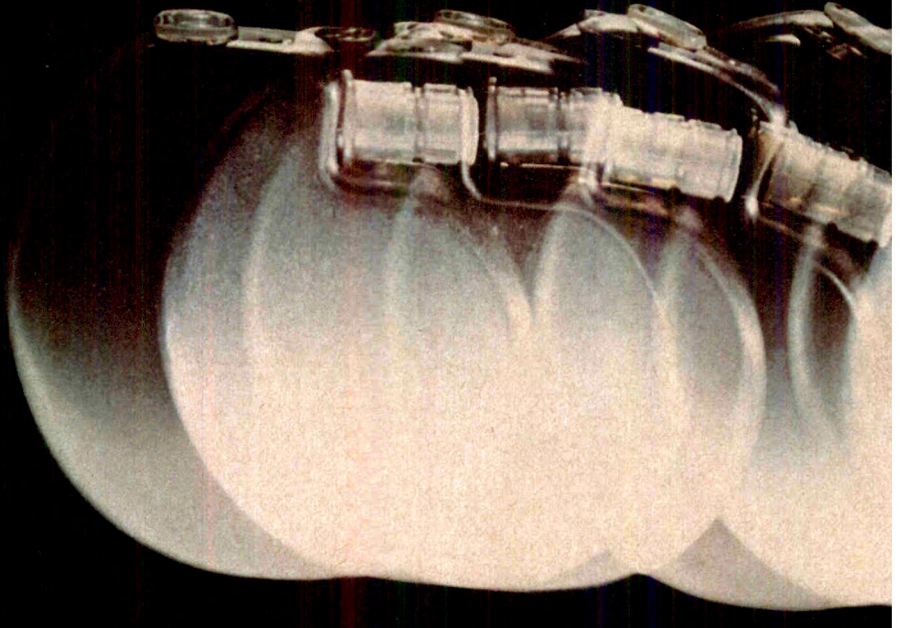
A SMALL REVOLUTION



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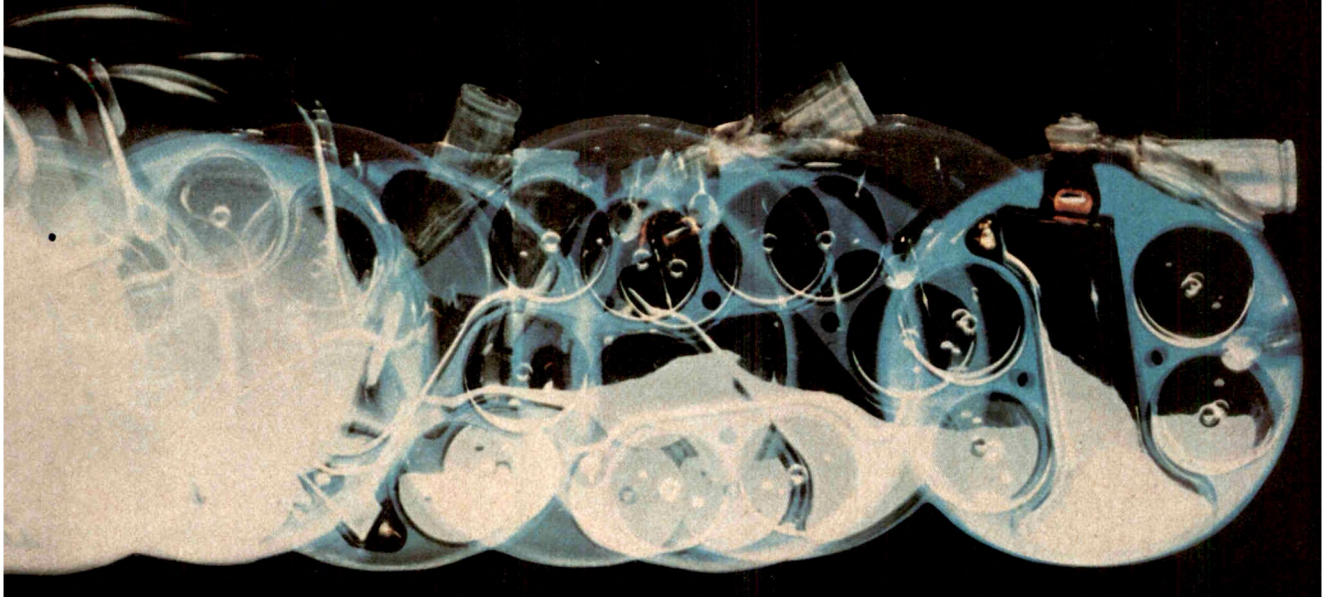

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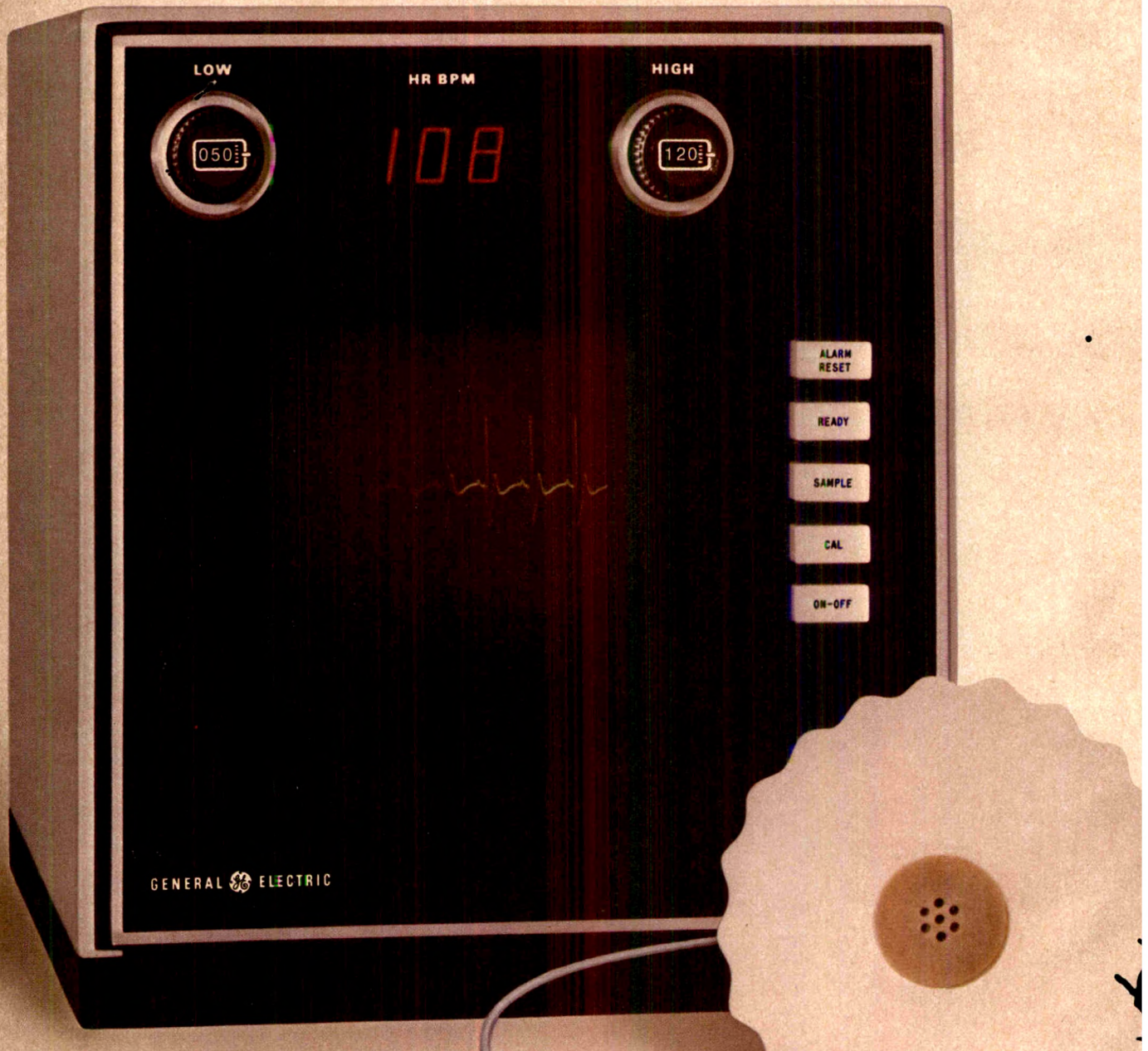

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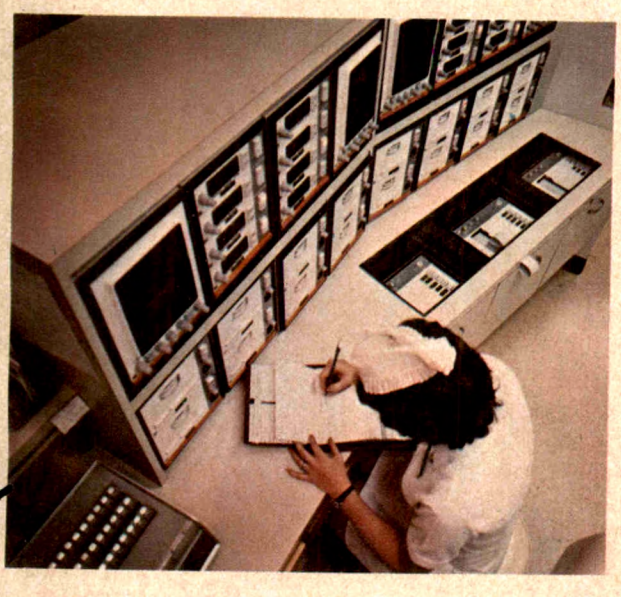

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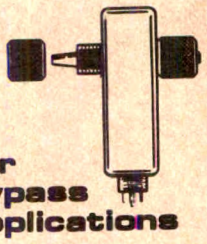

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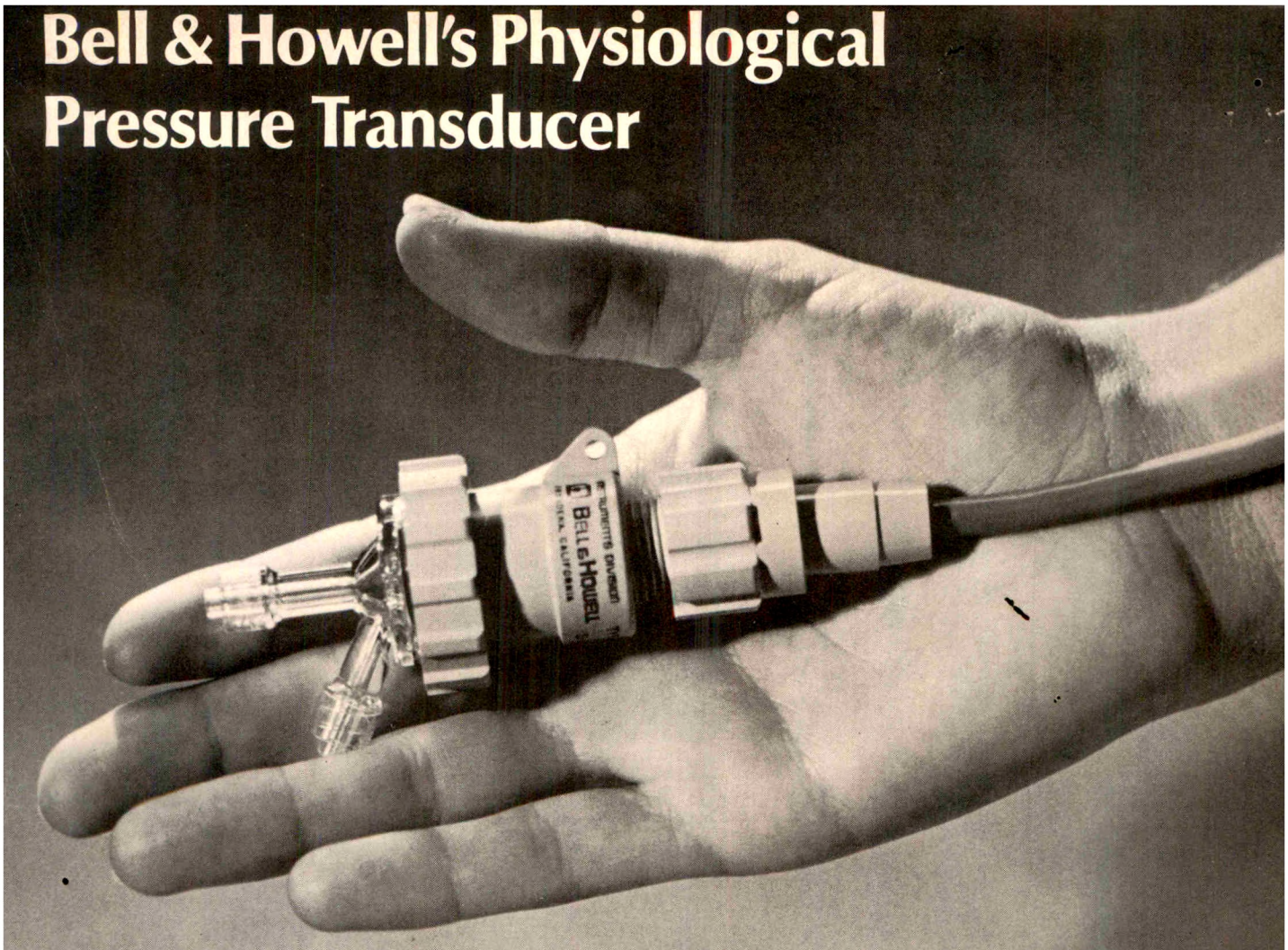

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy.

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Dyrenium (triamterene, SK&F) and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When Dyrenium is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.
Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 100 mg. capsules in bottles of 100; in Single Unit Packages of 100 (intended for institutional use only).

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